VOLUME 10 FEBRUARY 1961 NUMBER 1

# AUSTRALASIAN ANNALS OF MEDICINE

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The journal is published quarterly in February, May, August, and November. The subscription rate is four pounds per annum (one pound per issue), payable in advance to The Royal Australasian College of Physicians, 145 Macquarie Street, Sydney. The price of a single back number is twenty-five shillings. Advertising rates may be obtained on application to Australasian Medical Publishing Company Limited, Seamer and Arundel Streets, Glebe, Sydney.

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AUSTRALASIAN ANNALS OF MEDICINE

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# BREADTH AND DEPTH

*Pectus id est quod disertum facit.*

YOUNG graduates are not usually called physicians until they have been considered and approved by boards of censors or examiners. These boards require evidence that candidates have had training and practice in internal medicine in approved circumstances for an appropriate time. Indeed, during the recent Post-Graduate Conference on Medical Education in Sydney it was emphasized that the first five years of training for physicians should include not only clinical work in hospitals, but also training in the preclinical sciences, preferably in university departments. Candidates are also required to submit to a test, or tests, a pass in which is a *sine qua non* for acceptance as physicians. They must communicate to their examiners the fact that they have acquired enough information. To become physicians it is essential that young medical graduates are able to communicate at least with their examiners; they must be able to convey and receive information. In a broader sense this ability to communicate is a most important attribute of physicians, because it not only facilitates their scientific development and maintenance, but also contributes to their professional and teaching capabilities.

In recent years there has been a great deal of research into communication—the transmission and reception of information—and particularly into the scientific basis of it. The formal scientific treatment of the subject is referred to as "information theory", and a special terminology has been devised. Information theory concerns the amount of message, the number of "bits" of information, that can be carried over a transmission line in a given time. Information is coded into a message which is transmitted through one or more channels to a receiver, which is able not only to receive, but also to recognize the message. There is a limit to the amount of information that can be carried by a channel, and transmission systems differ in their efficiency and freedom from noise or error when different codes are used. "Redundancy" in a message means that it is not in the shortest possible form and, whilst it overloads the transmission channel, it can protect against noise and error. There is an inverse relation between length or complexity of a message and its reliability.

Since information theory forms the scientific basis of communication and since the ability to communicate is a desirable attribute of physicians, it is profitable to consider communicating physicians in terms of information theory, especially in regard to their development and training.

Would-be physicians, seeking approval by boards, must acquire enough "bits" of information, they must be prepared to transmit their messages through relatively noise-free channels without too much redundancy, they must transmit in synchrony with the receivers of their examiners, and they must use a code that the examiners recognize. The message is received and understood, a "pass" is recorded and the label of "physician" is applied and remains for life.

The new physicians' communication in regard to clinical medicine should improve, their messages become better coded and their channels less noisy, and some redundancy is beneficial. As age increases, both noise and redundancy increase, but physicians of the same age remain in communication with one another. For a while communication will be possible with younger physicians, but usually the codes of the basic sciences are lost and the channels to and from them become so noisy that communication is impossible, no matter how much redundancy is added for physicians.

It is important for physicians in training to get as much experience in the basic sciences as possible, so that, by relearning forgotten codes and by clearing noisy channels, they can communicate again. The longer they continue to communicate in the basic sciences, the longer they retain their scientific standing as physicians.

Young physicians usually interest themselves in a special field within internal medicine, be it academic medicine, clinical investigation or a specialty such as cardiology or hæmatology. In their chosen field they become better informed than their colleagues, and in general terms the specialty becomes their advertisement, the means by which they are known. In their fields of interest they develop highly specialized codes for their messages, they have noise-free channels and they avoid redundancy; but there will be relatively few receivers synchronized with their transmitters and able to understand their messages. The cardiologist understands the cardiologist, the hæmatologist the hæmatologist, but few physicians know more than one special code; a general physician may have difficulty with most or all of the special codes and channels. Unhappily, patients may be even more confounded than the general physician and get no message at all; they take comfort in their doctor's label of physician.

If advances in scientific medicine are to continue, specialization must continue and become narrower as it becomes deeper. Currently young physicians feel compelled to become specially well informed and skilled in a particular field, to learn a special code, to be able to communicate much information without redundancy to their colleagues in the same field. Careful plans are made to obtain early scientific training; training is directed to the acquisition of as much useful knowledge as possible. "Useless" knowledge, in Bertrand Russell's sense, is ignored, since its acquisition wastes time. They want to become filled with useful knowledge, to be complete in their special fields and attached to them.

It can be suggested that more scientific training is needed if young and middle-aged physicians are to continue to communicate effectively with colleagues in the preclinical sciences and to contribute to the advancement of scientific medicine. Many favour raising the required standards of physics and chemistry for freshmen entering universities and faculties of medicine in particular. Some have gone so far as to suggest that to reach the new standards, average boys and girls should start studying these subjects, rather than less scientific ones, at the age of 12 or 13 years. This particular raising of standards may facilitate the passage of students through medicine, it may raise the standard of medical graduates, and it may add something useful to the physician.

To these proposals should be added the suggestion that medical education, after the premedical year, is best carried out in a hospital medical school rather than on the university campus. It is maintained that within a hospital the medical atmosphere and the constant presence of patients and doctors would keep the practical applications of the preclinical sciences before students. Students could quickly learn medical codes and develop communication channels from their medically synchronized transmitters and receivers. Medical communication would be made easy, preclinical-clinical integration facilitated, and really firm attachments to medicine formed.

Implementation of these two proposals could aid the development of physicians with a scientific background and a strong attachment to scientific medicine; such physicians should be able to prepare and understand coded medical messages with little redundancy, and keep open channels to and from their medical and basic science colleagues. Their progress in deep specialization could be facilitated.

Will such a system, in which boys and girls of 12 or 13 are set on a medical course from which they may never deviate, necessarily produce the best physicians for the community or the best physicians as academic teachers? Certainly not, because physicians in contact with people, patients and students, need much more than a scientific outlook and training. Such physicians must be able to communicate with persons in all walks of life, with people of all ranges of intelligence and training; they must have codes and channels to use for messages transmitted to receivers with all sorts of synchronization and grades of understanding. They must have the means of clearing away the confusing effects of a noisy channel by adding appropriate redundancy to their messages or by using other codes and channels. If a patient fails to understand a doctor's message, it may well be because the doctor is not using the right code, or the right channel, rather than because the patient is stupid. If a student group seems dull and unresponsive, it may not be because of earlier poor teaching, of poor receivers, but because the present teacher is not transmitting receivable and understandable messages; he is using an ill-understood code, or there is too much noise on his channel.

It does not seem possible to supply physicians with the means of universal communication in their communities simply by adding courses to the medical curriculum. Much can be acquired in practice; but it has already been suggested that modern young physicians will spend more time in science and specializing, and less in the sort of practice that would give them multiple codes and channels as well as appropriate redundancy. It seems necessary to make sure that young physicians have some of these things before they start, seriously, their specialist and scientific training. There should be more opportunities for students to continue to acquire "useless" knowledge (which, in Bertrand Russell's sense, refers to knowledge which is not of direct utility by contributing to technical efficiency, but which is good of itself and, promoting a contemplative habit of mind, tends to create a broad and humane outlook on life in general), and more opportunities to associate with non-medical people—ends much better attained at a university than in a hospital. "Useless" knowledge adds a type of redundancy that can be improved upon only by mixing with people and sharing their problems. The incompleteness of university faculties, their need of each other, and the many student societies and activities, provide opportunities for medical students to acquire and develop interests outside medicine. University medical undergraduates can appreciate their incompleteness; they should easily acquire some "useless" knowledge and humanity to leaven their pure science. They may have noisier channels than they might have developed in a hospital medical school, but they will have more of them, more codes, and sufficient redundancy to transmit messages to many receivers. They need have no less scientific medicine; indeed, there are even greater opportunities to become familiar with the all-important pure sciences in a university than in a hospital.

It is questionable whether outside interests, a habit of acquiring "useless" knowledge and a real liking for people can all be acquired *de novo* at a university. It is probable that they must be obtained at least as attitudes at home and at school. There may be greater harm than good to future physicians if boys and girls substitute science for the humanities at an early age, even though such a policy may lead to more skilful laboratory scientists.

Physicians should be developed from boys and girls with broad educations in both the humanities and science, with wide interests in people and " things ", whose broad interests have been developed during their studies in a medical school within a university. They should have the opportunity not only to become highly trained in science, but also to follow their interests outside medicine.

Examining boards should use receivers of more than one kind in their tests on candidates before granting them the right to use the label of physician. Having established that the scientific codes, channels and transmission are adequate, they should demand messages over noisy channels, messages which are redundant, but which can be easily understood by patients and students. Members of examining boards should remember that more people understand and enjoy the redundancy of a fully orchestrated symphony than a perfect performance of a violin solo.

Can anyone be unmoved by the Song of Solomon ? Can anyone fail to understand it ? The clarity of its message is due to the richness of its language : it exemplifies depth with breadth, the ideal pattern of communication for physicians. " The heart is that which makes a man eloquent."

C. R. B. BLACKBURN.

# CUSHING'S SYNDROME

## THE VALUE AND LIMITATIONS OF STEROIDAL DIHYDROXYACETONES IN DIAGNOSIS[1]

A. W. STEINBECK[2, 3]

*From the Department of Medicine, University of Queensland*

SUMMARY

Nineteen cases of Cushing's syndrome have been studied. The clinical features before and after operation have been analysed. The plasma steroidal dihydroxyacetones (SDHA) have been estimated, before and after an intravenous infusion of corticotrophin when possible.

In Cushing's syndrome, plasma SDHA levels are likely to be raised, but may fall within the normal range or be doubtfully elevated. Also fluctuation in levels is possible. In hyperplasia, after corticotrophin the levels may progressively increase throughout the infusion, exceeding normal values throughout and with greater than normal increments in concentration. However, the individual levels, although raised, may not show the typical progressive increase : in some cases, they may even fail to show a normal increase. In a case of adrenocortical carcinoma, corticotrophin had no effect on plasma SDHA levels, and in a case of adenoma, the levels increased progressively throughout the infusion.

Difficulties in the interpretation of raised plasma SDHA levels are discussed. The possible value of SDHA estimations in differential diagnosis is indicated, and their limitations in diagnosis are also considered.

Studies with an 11β-hydroxylase inhibitor in the case of an adrenal adenoma are referred to, as well as the possible interpretations of the corticotrophin test after adrenalectomy.

Diagnostic difficulties are discussed briefly, and clinical reasons are given for preferring total to subtotal adrenalectomy in adrenocortical hyperplasia.

CUSHING'S SYNDROME is an uncommon disorder, which is sometimes diagnosed when in fact it does not exist. Cushing (1932) described only severe examples in his original report which, fortunately for the clinician, has emphasized a characteristic, familial appearance of those affected. This is more obvious in either long-standing or florid cases, although some characteristic features may be absent or minimal. Diagnosis is more often difficult in less typical and early instances, but, as the untreated disease has a poor prognosis (Cushing 1932; Plotz *et alii*, 1952; Sprague, 1953; Cope and Raker, 1955; Hurxthal and O'Sullivan, 1959), and with increased safety in its surgical treatment (Sprague, 1953; Bishop *et alii*, 1954; Cope and Raker, 1955; Montgomery and Welbourn, 1957; Mason *et alii*, 1958), there is a need for early diagnosis. The diagnosis should unequivocally exclude normal adrenocortical function, as adrenalectomy will lead to unnecessary hypocorticism under these circumstances.

The immediate cause of Cushing's syndrome is adrenocortical overactivity, no matter what the possible ætiological role of the anterior pituitary lobe, the hypothalamus or other tissues (Jailer *et alii*, 1956; Nelson *et alii*, 1960). The term Cushing's syndrome is possibly best reserved for cases presenting significant features of excess glucocorticoid activity, and the term hypercorticism (defining the nature of the over-activity) for those in which this does not apply (Sprague, 1953; Bayliss, 1957). Nevertheless, there is a distinct tendency to retain the eponymous term with a rather wider reference, although its application should logically be based upon excess glucocorticoid activity (Albright, 1943).

The following studies are reported to illustrate some features of the diagnostic pattern, and to indicate the possible variation in adrenocortical function that may be expected in the syndrome.

### METHODS

The subjects were either out-patients or in-patients referred for investigation. Cushing's syndrome was diagnosed on the basis of clinical

[1] Received on July 25, 1960.

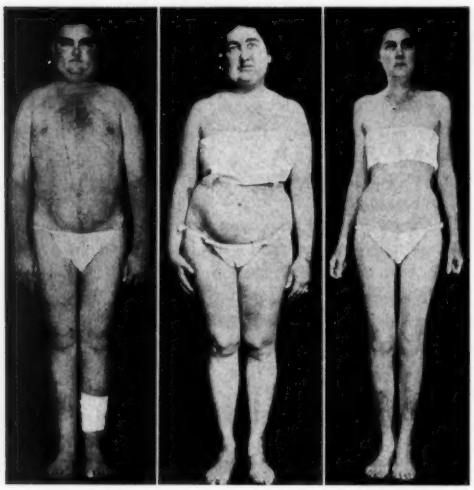
[2] Reader in Medicine, University of Queensland.

[3] In receipt of a grant from the National Health and Medical Research Council, Commonwealth of Australia.

[4] Read at a Plenary Session of the Endocrine Society of Australia with The Royal Australasian College of Physicians on May 25, 1960.

and laboratory features and the appearances of the adrenal glands, at operation and on examination of sections; the diagnosis was confirmed when regression of accepted features of the syndrome followed adrenalectomy.

Blood was collected mostly between 9 and 11 a.m. for isolated determinations of steroids. Because of the diurnal variation in plasma steroids, the concentrations in normal subjects tend to be higher at this time than in the late afternoon (Migeon *et alii*, 1956; Perkoff *et alii*, 1959). With a constant timing of the collections, it is unlikely that a day-to-day variation in the value would be solely due to a diurnal variation, should this occur in Cushing's syndrome.



(*a*) (*b*) (*c*)

FIGURE I

Presenting appearances of three patients. (*a*) Case 1: Showing the classical appearance of the syndrome; œdema of the hands and legs, in the absence of heart failure, can be discerned. (*b*) Case 9: Showing a relatively classical appearance; the legs are not thinned, but obesity is evident. (*c*) Case 12: Showing a thinned patient; supraclavicular pads are not present, nor was a cervico-dorsal hump; bruising of the legs can be discerned, and they were also œdematous

The technical procedures and methods of study have been described previously (Steinbeck, 1959), the terminology of steroidal dihydroxyacetones (SDHA) being used rather than 17-hydroxycorticosteroids.

## RESULTS

There were 19 patients with undoubted Cushing's syndrome, obvious clinically and confirmed in varying measure by steroid estimations, who with one exception have undergone some form of adrenalectomy.

### *Symptomatology*

The relevant symptoms and signs of these patients are analysed in Table I, and the presenting features of three (Cases I, IX and XII) are shown in Figures I, II, III and IV. The majority of the patients presented a typical appearance.

TABLE I

*The Symptomatology in the 19 Cases of Cushing's Syndrome*[1]

| Symptoms | Number of Cases | | Total Occurrence |
|---|---|---|---|
| | Presenting | Additional | |
| Fatigue and weakness .. | 7 | 10 | 17 |
| Depression and irritability | 2 | 11 | 13 |
| Changed appearance: .. | 2 | 16 | 18 |
| Mooned face or fullness of cheeks .. .. .. | 2 | 16 | 18 |
| Florid complexion[2] .. | 1 | 15 | 16 |
| Facial hirsutism in females .. .. .. | 4 | 9 | 13 |
| Truncal and related obesity[3] .. .. .. | 1 | 15 | 16 |
| Gonadal suppression[4] .. | 2 | 9 | 11 |
| Skin change: .. .. | 2 | 11 | 13 |
| Friability of any area .. | 1 | 1 | 17 |
| Poor healing .. .. | 1 | 3 | 4 |
| Skin infection .. .. | 3 | — | 3 |
| Purple or florid striæ .. | 2 | 11 | 13 |
| Rashes, excluding minor acne .. .. .. | — | 6 | 6 |
| Spontaneous or gross bruising .. .. | 2 | 7 | 9 |
| Back and bone pain .. | 2 | 5 | 7 |
| Ankle and hand œdema .. | — | 5 | 5 |
| Spontaneous fractures .. | 2 | 0 | 4 |
| Difficulty in walking .. | 4 | 1 | 5 |
| Generalized body aching .. | 2 | 2 | 4 |
| Arterial hypertension[5] .. | — | — | 18 |
| Radiological osteoporosis .. | — | — | 12 |
| Impaired glucose tolerance | — | — | 12 |

[1] In an attempt to decide which symptoms cause major concern to the patient, they are divided into presenting, or those forming a direct complaint by the patient, and additional, or those obtained by later questioning.
[2] Sometimes referred to as plum-coloured or tomato complexion.
[3] Including cervico-dorsal hump (not present in some) and supraclavicular pads.
[4] Impotence in males, menstrual disorders in females.
[5] Assessed both from change after adrenalectomy and as actual levels.

The duration of the illness varied. One patient complained of ill health for several months only, another for many years (probably exceeding 20), two for at least 11 or 12 years, the remainder for periods varying from less than one to several years. These estimates were checked against photographs and previous medical histories when possible.

Other symptoms than those listed were acknowledged. For instance, some patients had symptoms referable to hypertension—one had headaches and failing vision. Levels of

(*a*) (*b*) (*c*) (*d*)

FIGURE II

Facial appearances in Case 9: (*a*) and (*b*), before operation; (*c*) and (*d*), five months after operation. Scalp hair was still falling and cut short in (*c*) and (*d*); pigmentation was also present

arterial blood pressure were variable in one patient (Case 12, Table II); she was diagnosed elsewhere as suffering from progressive hypertension on the basis of significant hypertension (blood pressure 220/130 mm. Hg), left ventricular failure and prostrating headaches; eighteen months later her arterial blood pressure was mooned face were emphatic that the swelling fluctuated from day to day; this was confirmed in two while they were in hospital. The florid presenting features of the syndrome decreased in one case over a year, but bone and muscle changes continued. Two patients complained of skin friability, and 18 had skin offering little

(*a*) (*b*) (*c*)

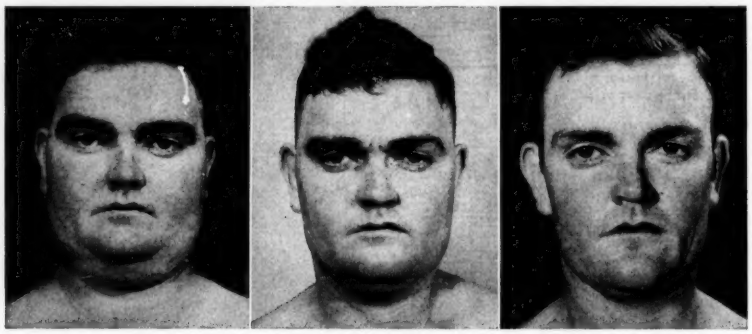
FIGURE III

Facial appearances in Case No. 12: (*a*) patient aged 29 years; (*b*) aged 43 years and before operation; (*c*) six months after operation

140/90 mm. Hg, and after a further twelve months 170/100 mm. Hg, without symptoms. In one case back pain was related to an adrenal tumour, rather than to the spine. One patient was particularly concerned about loss of weight.

With one exception, the patients admitted to a changed appearance, mostly confirmed by photographs. Moreover, some patients with a resistance to venepuncture. In most of these the skin was inelastic, as well as thinned, but was of fine tissue-paper quality in only one. Skin changes were mostly patchy in distribution. One patient, in whom bruising was gross, had tissue-paper skin solely on the legs and her only striæ were over the shins. Another had skin that was typically thinned over the forearms,

the lower part of the abdomen and the upper parts of the thighs, striæ being present in the abdomen; but the skin of the legs, which were œdematous, was thickened and toughened, and that of the chest, the shoulders and upper parts of the buttocks was porcine. These two patients had delayed healing of minor leg injuries, and the second was originally referred to a surgical ward for skin grafting to an indolent leg ulcer. This patient also had an extensive papular, scaling rash, involving the chest, back, shoulders and abdomen, which subsided after adrenalectomy. Three other patients had a similar rash, although less extensive and more discrete, and many had minor acne. All the women had facial hirsutism, varying from a readily noticeable moustache, cheek and chin hair to a heavy beard in association with frontal recession of hair, but none had a deepening of the voice or clitoral enlargement. The patient whose skin was not thinned was heavily hirsute. Two of the patients with heavy hirsutism lost most of the excess within several months of adrenalectomy. One male, in whom the syndrome had a pubertal onset, said that he had recently lost body hair. Although he did not have gynæcomastia, his testes were flabby; after adrenalectomy they became firm and his body hair heavy, and he developed male baldness.



(*a*) (*b*) (*c*)

FIGURE IV

Facial appearances in Case 1: (*a*) before operation, showing classical facial alterations of the syndrome; (*b*) three and a half months after operation, showing the tired appearance of the patient when withdrawal symptoms were still troublesome; the patient doubted the benefit of the operation at this time; (*c*) 12 months after operation, showing subsequent regression of condition in relation to facial appearances; recession of scalp hair is now evident

Muscle wasting, and particularly fatigue, were constant features. One patient was forced to receive ambulance aid because of an inability to ascend public steps; two others were barely able to walk, and one could not walk at all up stairs, pain on walking being an added factor. Two of these patients noted that painful weakness of the back was particularly disabling. Back weakness led to poor posture in some patients; in three this was striking, with alteration of spinal curvature, and, combined with weakness of the legs, it led to a distinctive disturbance of gait. Presentation was determined by spontaneous fractures in two patients, and nursing procedures precipitated further rib fractures and a vertebral crush-fracture in another. Radiologically evident osteoporosis was not constantly present, but in two cases it was severe and associated with spinal shortening, with crushed vertebræ; one of these patients was aware of a definite loss of height. Some patients complained of body aching, which was not easily localized to bone and seemed muscular; two patients differentiated between actual bone pain and this aching. Bone pain was distressing to certain patients; one had noticed increasing pain for some time, with weakness before spontaneous fractures developed, and another described distressing pains in all bones, with intense aching localized to the joints and a sensation of the pelvic bones giving way on walking. She thought of her predicament as one in which the bones were gradually dissolving painfully away, and doubted her ability to adjust any further to bone, muscle and joint pains. In one case bone pain was due to low-grade osteomyelitis. One patient (Case 1), whose disease was pubertal in onset, was considerably shorter than his siblings and

parents, and was known to have grown only slowly.

Most patients had bruising of varying severity, and in two this was severe and led to early investigation, without recognition of the cause. In one there was also a Majocchi-like purpura of the legs, which were pigmented from old bruises. No patient had significant polycythæmia, but absolute eosinopenia was present in some. A low serum potassium concentration associated with a convincingly raised serum bicarbonate level was infrequent. Glycosuria was also infrequent, but was the reason for one patient's rejection from military service without recognition of the cause; clinical diabetes mellitus occurred in only one subject, although impaired glucose tolerance was not uncommon. Of three patients who were examined for evidence of thyroid suppression, when thyroid uptakes of radio-iodine before and after adrenalectomy were compared, only one showed a significant increase in uptake after adrenalectomy. The consequences of the defect, if any, would have been overshadowed by grosser clinical changes.

Mental symptoms were striking in several cases, and of psychotic character in two. Two patients were distressed by loss of mental alertness, and mentation was considerably clearer in several after clinical cure. A number of patients were irritable, one aggressively so, and others were depressed; in three irritability tended to alternate with depression. In two hebetude was considerable and associated with drowsiness.

After operation, most patients who could be adequately followed up and in whom regression of the condition became striking, developed itchiness of the skin, often with papular erythema, and later fine desquamation. A number of patients developed grey-blue mucosal patches, some dark operation scars and two intense skin pigmentation shortly after operation, although receiving 50 to 75 mg. of cortisone daily by mouth. If the patient in Case 4 is disregarded, none of the patients who developed pigmentation after operation have shown a discernible increase in size of the pituitary fossa; however, pigmentation subsequently lessened in most. Two patients showed a definite regression of the condition in relation to facial appearances and supraclavicular pads after the first stage of adrenalectomy. Facial and body hair was lost by some women, and a loss of scalp hair preceded its regrowth in several cases. One patient (Case 12), who had noted an apparent menopause, started to menstruate regularly, at first excessively, shortly after adrenalectomy. Another patient (Case 1) finally developed heavy body hair after adrenalectomy, with further secondary sexual development and adult differentiation of the facies. His hebetude also disappeared, and he became able to manage a dairy-farm. Two patients developed minor depression after operation, in one case related to hypocorticism; mostly the patients with mental symptoms showed gradual improvement after adrenalectomy. The increased efficiency of a secretary was particularly striking. Most of the patients who could be adequately followed up complained of cortisol withdrawal symptoms for varying periods, although none of those tested had hypercalcæmia. The time of full convalescence was variable, ranging from four months to two years.

TABLE II

*Isolated Determinations of Plasma SDHA Concentrations in Cushing's Syndrome*

| Case Number | Subject's Sex and Age (Years) | Treatment[1] | Appearance of Glands | Plasma SDHA Concentration (µg. per 100 ml.) |
|---|---|---|---|---|
| 1 | M. 24 | TAx | Hyperplasia | 34·2 |
| 2 | M. 34 | SAx | Normal | 28·8 |
| 3 | M. 24 | SAx | Normal | 19·2 |
| 4 | M. 23 | SAx | Hyperplasia | 22·8 |
| | | | (Five days later) | 20·7 |
| 5 | M. 34 | SAx | Hyperplasia | 28·8 |
| 6 | M. 27 | SAx | Hyperplasia | 20·7 |
| 7 | F. 45 | SAx | Hyperplasia | 12·4 |
| | | | (Four days later) | 20·2 |
| 8 | F. 40 | SAx | Hyperplasia | 22·4 |
| | | | (Two and three weeks later) | 8·8<br>6·2 |
| 9 | F. 35 | TAx | Nodular hyperplasia | 24·5 |
| 10 | F. 48 | TAx | Carcinoma | 51·2 |
| 11 | F. 46 | TAx | Carcinoma | 31·1 |
| 12 | F. 43 | UAx | Adenoma | 30·1 |
| | | | (Three weeks later) | 24·9<br>28·6 |
| 13 | F. 43 | — | —— | 27·0 |
| | | | (Six weeks later) | 18·0 |
| 14 | F. 62 | SAx | Hyperplasia | 34·5 |
| | | | (Two weeks later) | 36·1 |
| 15 | F. 63 | SAx | Nodular hyperplasia | 24·2 |
| 16 | F. 52 | SAx | Hyperplasia | 80·0 |
| 17 | F. 26 | SAx | Normal | 29·6 |
| 18 | F. 47 | SAx | Not recorded | 20·1 |
| 19 | F. 42 | SAx | Adenoma | 16·5 |

[1] TAx, SAx, UAx = total, subtotal, unilateral adrenalectomy, respectively.

### *Operative Findings*

*The Adrenal Glands.*—The appearances of the adrenal glands are indicated in Table II. One malignant tumour was macroscopically obvious as such, the other only on histological examination. Two patients had a benign adenoma, although one could be described only as small; two had definite nodular hyperplasia (Mosier *et alii*, 1960). Eight had so-called macroscopic hyperplasia in terms of comb thickness of the gland (Cope and Raker, 1955), itself not necessarily overweight, and in three

the glands appeared normal on examination of sections and in routine histological preparations. Not all glands were weighed; of those examined, weights varied from 18 grammes to "massive", for a carcinoma. In the remaining two cases the nature of the glands is unknown because of the absence of operative findings.

*The Ovaries.*—In two patients examined (Cases 9 and 12) the ovaries were paler, firmer, and larger than normal. The capsule was denser than normal, there were many cysts containing small amounts of fluid and abnormal thecal cells were present.

### *Steroid Determinations*

*Isolated Determinations of Plasma SDHA Concentration.*—For the normal plasma concentration range of SDHA, reproducibility is such that a difference of 3·5 μg. per 100 ml. of plasma between duplicate estimates is significant ($P=0·05$). Normal plasma contains 2·5 to 19·0 μg. of SDHA per 100 ml. in the morning after 9 a.m., the distribution being skew; the mean value is within the range 9 to 10 μg. per 100 ml. of plasma. The values, mostly estimated in duplicate and some by two methods, are shown in Table II. In 12 cases (1, 2, 5 and 9 to 17), the concentrations are convincingly greater than 19 μg. per 100 ml. on one occasion, and so are elevated. In one case (19) the concentration was within the normal range, and in another (Case 3) at the upper limit of normal on the only occasion on which plasma was obtained. In five cases (4, 6, 7, 8 and 18) the values were just outside the normal range, suggestively or doubtfully elevated, on at least one occasion. Normal values were found on other occasions in two of these (Cases 7 and 8), and in another case (13) after a high initial value.

*The Alteration in the Plasma SDHA Concentration after an Intravenous Infusion of Corticotrophin.*—Only seven patients could be studied in this way, and the additional results are shown in Table III. In the patient (Case 11) with a large adrenal carcinoma, there was no change in steroid concentration after the infusion, and plasma levels appeared to be constant, within the limits of the method, over two days, suggesting an absence of diurnal variation. In the patient (Case 12) with a moderate-sized benign adenoma (Figure V), the increment in concentration of plasma steroids after six hours of infusion was at the upper limit found in normal subjects, although the absolute levels were higher and increased progressively during the infusion. In one patient (Case 1) with hyperplastic glands, plasma steroid levels that were initially raised did not increase by even a normal amount after corticotrophin had been given, and failed to exceed values that might be expected in normal subjects. In another patient (Case 7) with hyperplastic glands, the increase in plasma steroid concentration after two hours of corticotrophin infusion was considerable, an abnormally rapid as well as an excessive increase; but a progressive increase did not occur during the infusion, although high steroid levels were maintained. In the three remaining patients (Cases 4, 8 and 9) with hyperplastic adrenals, there was a progressive rise in the plasma steroid levels throughout the infusion; after six hours of infusion they exceeded 70 μg. per 100 ml., levels considerably in excess of those expected in normal subjects. The increments were 57·8, 73·4 and 48·3 μg. per 100 ml. of plasma upon equivocally normal, normal and raised initial values, respectively, and exceeded the upper normal limit of 30 to 35 μg. per 100 ml. The response in one of these cases (8) is important, as initial values were low on the day of the infusion.

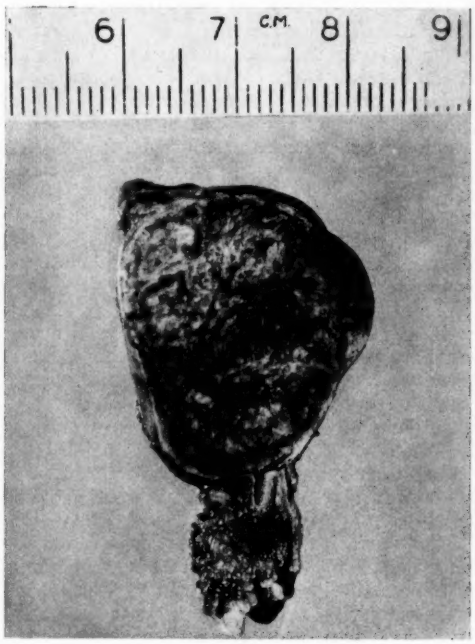



FIGURE V

A cross section of the adenoma removed in Case 12

After subtotal adrenalectomy, a corticotrophin infusion led to an increase in the plasma steroid levels in the only subject who could be tested (Case 4), but the concentrations were at the lower limit of normal and the increment was less than normal. After unilateral adrenalectomy, the remaining adrenal gland did not respond to corticotrophin in Case 12.

TABLE III

*Plasma SDHA Concentrations after Corticotrophin Infusion in Cushing's Syndrome*[1]

| Case Number | Corticotrophin (I.U. per Hour) | Plasma SDHA (µg. per 100 ml.): Hours 0 | 2 | 4 | 6 | 8 |
|---|---|---|---|---|---|---|
| 1 .. .. | 2·5 | 34·2 | — | 43·5 | 42·8 | — |
| 4 Before operation .. .. | 2·0 | 20·7 | — | 56·1 | 78·5 | — |
| Eight months after operation .. .. | 2·0 | 11·2 | — | 22·0 | 21·5 | — |
| 7 .. .. | 2·0 | 20·2 | 58·5 | 62·8 | 75·5 | — |
| 8 .. .. | 2·0 | 6·2 | 25·6 | 64·5 | 79·6 | — |
| 9 .. .. | 2·5 | 24·5 | — | 54·2 | 72·8 | — |
| 11 .. .. | 2·5 | 31·1 | — | — | 35·5 | — |
| 12 Before operation .. .. | 2·5 | 30·1 | — | 46·5 | 59·2 | — |
| Six weeks after operation .. | 2·5 | 0·5 | 2·4 | 1·4 | 1·4 | 4·8 |

[1] Corticotrophin was given in an intravenous infusion at a constant rate over eight hours.

*Isolated Determinations of Plasma SDHA Concentration after Subtotal or Unilateral Adrenalectomy.*—These are shown in Table IV. The values were lower than before operation in all, but less than normal in two (Cases 12 and 17).

TABLE IV

*Isolated Determinations of Plasma SDHA Concentrations after Adrenalectomy for Cushing's Syndrome*

| Case Number | Plasma SDHA Concentration (µg. per 100 ml.) | Post-Operative Interval: Weeks | Months |
|---|---|---|---|
| 4 | 9·4 | 2 | — |
| | 9·9, 8·8, 11·2 | — | 1, 2, 8 |
| 12 | 0, 0·5 | 4, 6 | — |
| 14 | 7·5, 16·8 | 2, 4 | — |
| | 9·3 | — | 5 |
| 16 | 8·6 | — | 4 |
| 17 | 2·6 | 6 | — |

The response to corticotrophin confirmed hypocorticism in Case 12 (see Table III); but substitution therapy was started before the response of the remnant could be tested in the other, because of clinical hypocorticism.

*Isolated Determinations of Plasma SDHA Concentration in Distressed Subjects.*—These are listed in Table VA. Three subjects (Cases 20, 21 and 22) were normal males, and when each became irritated or upset for various reasons steroid levels were higher than at similar or earlier times of day under equitable conditions. The difference between paired values would be reduced by accepting control values from earlier times of day because of the diurnal variation in plasma SDHA levels (Perkoff *et alii*, 1959). Three more subjects (Cases 23, 24 and 25) showed a similar change while awaiting a painful and unknown procedure, respectively. Three further subjects (Cases 26, 27 and 28) had higher levels during actual pain than normally.

TABLE V

TABLE VA

*Plasma SDHA Concentrations in Distressed Subjects*

| Case Number | Subject's Sex and Age (Years) | Plasma SDHA (µg. per 100 ml.): Control Value[1] | "Distressed" Value | Reason for Distress |
|---|---|---|---|---|
| 20 | M. 33 | 8–12 | 22·4 | Irritation |
| 21 | M. 46 | 8– 9 | 22·9 | Irritation |
| 22 | M. 27 | 8–10 | 26·9 | Irritation |
| 23 | M. 18 | 5– 7 | 28·4 | Apprehension |
| 24 | F. 27 | 10–14 | 26·8 | Apprehension |
| 25 | M. 60 | 5– 6 | 18·6 | Apprehension |
| 26 | F. 71 | 9–15 | 50·3 | Pain |
| 27 | F. 73 | 11–16 | 25·5 | Pain |
| 28 | M. 42 | 15 | 39·0 | Pain |

[1] Control values were obtained at similar or earlier times of day than the "distressed" values. In the latter case, any bias would favour a reduction of the difference (Perkoff *et alii*, 1959).

TABLE VB

*Plasma SDHA Concentration after Corticotrophin in Patients Distressed by Pain for Some Days*

| Case Number | Subject's Sex and Age (Years) | Corticotrophin (I.U. per Hour) | Plasma SDHA (µg. per 100 ml.): Hours 0 | 2 | 4 | 6 |
|---|---|---|---|---|---|---|
| 29 | M. 53 | 2·5 | 15·6 | — | — | 73·6 |
| 30 | F. 73 | 2·5 | 15·9 | — | — | 66·5 |

*The Alteration in the Plasma SDHA Concentration after an Intravenous Infusion of Corticotrophin in Subjects Who had Experienced Pain.*—The results for two patients are listed in Table VB. The levels attained and their increment, upon apparently normal initial values, were greater than in normal subjects.

*Isolated Determinations of Plasma SDHA Concentration in Patients Suspected of Having Cushing's Syndrome.*—These are shown alongside clinical details of 10 selected cases in Table VI. The levels were normal on the occasion of the estimation in eight cases, and elevated on the first occasion in the tenth case (33) but normal on the second, when the patient was not distressed.

TABLE VI

*Isolated Determinations of Plasma SDHA Concentrations in Patients Referred for Differential Diagnosis of Suspected Cushing's Syndrome*[1]

| Case Number | Subject's Sex and Age (Years) | Plasma SDHA Concentration (μg. per 100 ml.) | Glycosuria | Impaired Glucose Tolerance | Cutaneous Striæ | | Hypertension[2] | Suggested Diagnosis[3] |
|---|---|---|---|---|---|---|---|---|
| | | | | | Pale | Livid | | |
| 31 | M. 30 | 15·9 | + | + | + | o | + | Obesity and essential hypertension |
| 32 | M. 29 | 13·7 | o | o | + | o | ± | Obesity and reactive depression |
| 33 | M. 26 | 33·8 | o | + | + | o | ± | Obesity |
| | | 2·4 (Three weeks later) | | | | | | |
| 34 | F. 67 | 10·4 | + | + | o | + | + | Obesity and polycythæmia vera |
| 35 | F. 45 | 8·4 | + | + | + | o | + | Obesity and essential hypertension, hirsutism |
| 36 | F. 39 | 3·9 | + | + | + | o | o | Obesity and hirsutism |
| 37 | F. 42 | 12·4 | + | + | + | o | + | Obesity and hirsutism |
| 38 | F. 19 | 24·9 | ± | + | + | + | + | Obesity and hirsutism |
| 39 | F. 53 | 14·0 | o | + | + | o | + | —— |
| 40 | F. 46 | 15·9 | ± | ± | + | o | ± | —— |
| | | 10·7 (Four days later) | | | | | | |

[1] Features are recorded as absent (o), doubtful or inconstant (±), present (+), and impairment of glucose tolerance is scored as "+" or "o".
[2] "±" refers to labile arterial blood pressure.
[3] Hirsutism refers to significant hairiness, probably developmental in Case 35 and familial in Case 38.

*Determinations of Plasma SDHA Concentration Before and After an Intravenous Infusion of Corticotrophin, in Patients Presenting a Diagnostic Problem with Regard to Cushing's Syndrome.*—Seven patients are included in Table VII, the first two also being shown in Table VI. Two patients (Cases 39 and 40) had normal initial levels; the increment after corticotrophin administration was normal in Case 39, but the actual concentrations attained, and their increment upon the initial value, were just without the normal range in Case 40. Two more patients (Cases 41 and 44) had raised initial levels, and one patient (Case 43) had a doubtfully raised one, but the concentrations and their increment upon the initial value were considerably above the normal range. The only value obtained in Case 42 was raised and that in Case 45 was within normal limits.

TABLE VII

*Plasma SDHA Concentration in Patients with an Equivocal Differential Diagnosis*[1]

| Case Number | Subject's Sex and Age (Years) | Plasma SDHA Concentration (μg. per 100 ml.): Hours | | |
|---|---|---|---|---|
| | | o | 4 | 6 |
| 39 | F. 53 | 14·0 | 29·4 | 40·0 |
| 40 | F. 46 | 15·9 | 38·9 | 52·4 |
| 41[2] | F. 20 | 24·2 | — | 73·0 |
| 42[3] | F. 26 | 22·4 | — | — |
| 43 | F. 22 | 19·8 | — | 82·2 |
| 44 | F. 27 | 28·6 | 57·2 | 66·7 |
| | One month after SAx[4] | 10·2 | 9·9 | 13·1 |
| 45 | M. 43 | 17·8 | — | — |

[1] Corticotrophin was given in an intravenous infusion at a constant rate of 2·5 I.U. per hour.
[2] Ten weeks pregnant.
[3] Twelve weeks pregnant.
[4] Subtotal adrenalectomy.

## DISCUSSION

The clinical variation in Cushing's syndrome in these cases is, on the whole, not greatly dissimilar from that in other series (Knowlton, 1953; Sprague, 1953; Cope and Raker, 1955; Soffer *et alii*, 1955; Querido and van Seters, 1956; Montgomery and Welbourn, 1957; Hurxthal and O'Sullivan, 1959). Pregnancy did not precede the onset in any case, which is probably related to the menstrual history and marital status of the women. Most of the patients had a characteristic familial resemblance to one another (Cushing, 1932). None of the patients had evidence of liver disease or a raised blood urea level (Samuels, 1957).

### *Symptomatology*

It does seem that an indeterminate course is uncommon. Mostly, the onset and course of the disease can be described in terms of slowness or rapidity, and of progression and possibly fluctuations in some patients, though fluctuations in individual features are more convincing. For instance, the arterial blood pressure varied considerably in Case 12, but although the patient became less florid, loss of weight and bone and muscle changes were progressive. Although the course of the syndrome is variable, and may indeed be fluctuant, it is difficult to conceive of actual transiency as recorded by Zondek and Leszynsky (1956). However, fluctuation in

features of the disease and adrenal secretion is well authenticated (Birke *et alii*, 1956; Bassöe *et alii*, 1958). That the syndrome can persist unrecognized for some years, even though medical attention is sought, is evident from the 11 to 12 years history in Case 1, and, equally important, that the patient may accept disability for many years is evident from the long history in Case 14. Although there is a classical picture of the syndrome, there can be a diversity of appearance and a fluctuation, which seem responsible for certain features not being accorded due significance. Then, investigation of such isolated features as gross bruising, hypertension, menstrual disturbances, etc., can occur. In this regard, a long interval of unrecognized disease has been associated with a slow progression and prolonged absence of asymmetrical truncal obesity; indeed, surgery was carried out on some patients for incidental reasons, the sutures tearing thinned skin in one, and the scars later widening into typical Cushing's striæ without being recognized as such.

The most persistent complaint was fatigue with weakness, concern over changed appearance being less. The chief symptoms were fatigue with weakness, a characteristic alteration in appearance and truncal obesity with relatively specific skin changes and an irritable depression (Knowlton, 1952; Starr, 1952; Querido and van Seters, 1956) or blunting of personality. The association of these features with arterial hypertension, osteoporosis or bone pain and impaired glucose tolerance presents little diagnostic difficulty. However, obesity may not be present, rather general wasting (Montgomery and Welbourn, 1957), and it seems that the dominance of less common symptoms is particularly confusing in these circumstances.

Such considerations are well exemplified in Case 12 (Figures I and III); this patient was wasted, and had become progressively so over three or four years. Her illness seemed intermittent, particularly hypertension and mental depression, which were regarded as reactive to her domestic situation but remitted spontaneously. Initially, she complained of severe hypertensive symptoms (blood pressure 220/130 mm. Hg) and hæmatemesis; with the development of joint pains, purpura, bruising and skin changes, her physician thought a collagen disease existed. Subsequently, she attended another physician on two occasions at an interval of 12 months; on the first, she complained of bruising and purpura with orthostatic œdema and leg aches, not referred to bone, but there was no hypertension (blood pressure 140/90 mm. Hg); on the second, her facial changes were less florid, she had extreme difficulty in walking, because of bone and muscle pains as well as weakness, she was mildly hypertensive (blood pressure 170/100 mm. Hg) and the personality changes present on the first examination were obvious in retrospect with their remission. In this way the significance of the initial complaints was recognized, but her disease required four years for diagnosis. In the interval she had consulted an orthopædic surgeon because of intense bone pains and difficulty in walking.

It is of some interest that Querido and van Seters (1956) indicate that some patients who were only slightly overweight had severe clinical symptoms.

There were less common features in individual cases. Bruising is known to be a common feature of the syndrome, but two patients had sufficiently intense bruising for it to be investigated independently, particularly as it appeared spontaneous; one (Case 12) had an initial hæmatemesis and soon after developed hæmorrhoids which bled easily and frequently. She also bled profusely and for long periods after minor trauma, and bleeding frequently restarted after its apparent cessation, an abnormality related to vessel walls. Three patients had evident exophthalmos (Plotz *et alii*, 1952; Querido and van Seters, 1956; Morgan and Mason, 1958), but proptosis was not sought in other patients. One patient stated that her skin had become darker soon after she noted her changed appearance; this was difficult to evaluate because of her racial origin, but there was no enlargement of the pituitary fossa (Salassa *et alii*, 1959). No patient appeared to have renal calculi (Hurxthal and O'Sullivan, 1959), although two were known to have an increased urinary excretion of calcium. One patient failed to attain body height compatible with his family background; his disease was pubertal in onset, and he had some loss of masculinization; he showed improvement in thyroid uptake of radio-iodine after adrenalectomy. In his case the clinical features might suggest pituitary hypofunction in the presence of excess cortisol production. In the absence of œstrogen determinations, the cause of his loss of masculinization can only be assumed, but he did not have gynæcomastia or œstrogenized nipples. Another male patient, aged 61 years, not referred to in this series, who was moribund soon after his admission to hospital, and who presented initially with clinical diabetes mellitus, had become feminized before his final admission, with gynæcomastia and œstrogenized nipples, atrophy of the penis and testes, loss of body hair, etc. He was pigmented and at post-mortem examination was found to have a pituitary basophil adenoma (Salassa *et alii*, 1960). In addition, he was the only patient in whom a severe infection became a problem, and the cause of his death.

After operation, it seemed that the times of convalescence were related to the length of the

history and the intensity of disease, as well as to the control of withdrawal symptoms. One patient with an 11 or 12 years' history required nearly two years for attainment of normal living, one with a 15 to 18 months' history required six months, and a third patient (Case 12) required 12 months. These three patients commenced full replacement doses of cortisone soon after adrenalectomy. Post-operative skin changes were similar to those previously described (Cope and Raker, 1955; Mason, 1957; Montgomery and Welbourn, 1957). Persistent pigmentation after adrenalectomy occurred in one patient, who did not sunbake, on full cortisone replacement and has caused some mental distress, particularly as acrocyanosis also developed. This pigmentation can be compared with that in a patient, not referred to in this series, who refused the second stage of adrenalectomy and has subsequently become pigmented, although she has a normal resting urinary output of steroids. The most striking pigmentation developed in another patient not referred to in this series, after a subtotal adrenalectomy and subsequent loss of the adrenal remnant by infection; cortisone replacement had little effect on her pigmentation, and facial hirsutism increased with higher dosage. Neither of these two patients shows an increase in size of the pituitary fossa over some years, which probably excludes a significant pituitary tumour (Nelson *et alii*, 1960) but not compensatory hyperfunction (Salassa *et alii*, 1959). Patients with ankle and hand œdema continued to have this for some months after operation.

Withdrawal symptoms have occurred in a number of patients during the post-operative metabolic adjustment to lowered steroid levels. In the post-operative period, bone and joint aching has become accentuated in several patients, requiring time for their relief; in each case nor-androstenolone phenyl-propionate ("Durabolin"—Overbeek and de Visser, 1957) was given by intramuscular injection. In Case 12 these pains persisted for some nine months. The acute withdrawal symptoms were mainly nausea and anorexia, which interfered with feeding in some cases, as well as weakness not related to orthostatic hypotension; the basis of the bone aching is not obvious, and it is difficult to accept recalcification (Cope and Raker, 1955) as its cause. Also one patient found muscle aches and cramps distressing for many months; these were not related to electrolyte disorders.

### *Operative Findings*

The appearances of the adrenal glands are not dissimilar from those of the series already referred to. The findings in the ovaries, in the two cases tested, are similar to those in the case reported by Birke *et alii* (1956) and in other types of adrenal hyperfunction (Perloff *et alii*, 1958).

### *Steroid Results*

*Plasma SDHA Concentrations in Cushing's Syndrome.*—The method measures free steroids, but does not differentiate between cortisol and its metabolites; also it does not indicate what fraction of cortisol is freely diffusible or tissue-active, and therefore involved in hormonal regulations (Sandberg and Slaunwhite, 1959; Slaunwhite and Sandberg, 1959). The earlier method used (Bayliss and Steinbeck, 1953) would have estimated 11-desoxycortisol if present, but the later method (Steinbeck, 1959) does not adequately recover it (Gold *et alii*, 1960); recovery rates for cortisol are 90% to 100% and 65% to 80% for 11-desoxycortisol (Steinbeck and Yarrow, unpublished).

In Cushing's syndrome, plasma levels of SDHA are likely to be raised, but in some cases they may fall within the normal range for the method, and on occasions their increase above normal may not be sufficient for confident interpretation. Some cases show extreme fluctuation in plasma levels, from high values to below the mean normal value (Table II). In this regard, extreme fluctuations in the urinary excretion of 17-ketogenic steroids, and also features of the disease, have been demonstrated in single cases of adreno-cortical hyperplasia by Birke *et alii* (1956) and by Bassöe *et alii* (1958), and such fluctuations have been previously described for other steroids, as the authors indicate. It is probable that such changes reflect variations in adreno-cortical activity; but plasma steroid levels are the resultant of steroid secretion, utilization and excretion, and their variation may represent some change in the other factors, although lasting changes suggest variations in adreno-cortical activity. Some cases show a relative constancy in plasma SDHA levels—a range not exceeding 5 μg. per 100 ml. of plasma over four weeks in Case 12, two weeks in Case 14 and five days in Case 4. Other data suggested that there was little variation in plasma levels over one day in Cases 4, 11, 12 and 14. In this regard, Lindsay *et alii* (1956), Cohen *et alii* (1958) and Doe *et alii* (1960) have demonstrated an absence of the diurnal variation of plasma SDHA levels in some cases of Cushing's syndrome. Doe *et alii* (1960) have also shown that a restricted diurnal variation may occur in other cases; this seemed possible in view of the

considerable day-to-day variation of plasma steroid levels in some cases.

The highest and lowest steroid concentrations, 80 and 6·2 μg. per 100 ml. of plasma respectively, were found in cases of adrenal hyperplasia. The two patients with carcinoma had intermediate levels, significantly raised, and those with an adenoma had a normal and a raised level, respectively. Not unexpectedly, an isolated steroid determination gives no indication of adrenal pathology. Of some importance are the near-normal and normal values occurring in some instances of the syndrome. There seemed no constant relationship between plasma steroid levels and the twenty-four hour urinary excretion of steroids. For instance, one patient (Case 1) with raised plasma levels of SDHA, had urinary outputs of 17·8 to 18·2 mg. of 17-ketosteroids (17-KS) and 14·1 to 15·1 mg. of 17-ketogenic steroids (17-KGS) per 24 hours, respectively, or normal values; a second patient (Case 12) excreted 8·0 mg. of 17-KS and 21·5 mg. of 17-KGS, respectively (a normal 17-KS output and a somewhat raised 17-KGS value). This may be described as a plasma-urine dissociation; Christy *et alii* (1955) found the plasma steroid level more informative than the urinary excretion of steroids in some cases. In general, the urinary excretions of 17-KS were not increased as often as the plasma levels of SDHA, but in both cases of carcinoma 17-KS excretions were increased—a common finding (Cope and Raker, 1955; Bayliss, 1957). Other urinary steroid groups seem more informative than 17-KS, and probably 17-KGS (unpublished data).

*Plasma SDHA Concentrations after Corticotrophin Infusion in Cushing's Syndrome, Before and After Adrenalectomy.*—The greatest increases in concentration appear to occur in adrenal hyperplasia, a progressive rise during the infusion with the several levels absolutely higher than normal being characteristic. This has been noted by others (Christy *et alii*, 1955; Eik-Nes *et alii*, 1955; Grumbach *et alii*, 1955). However, this is not constant, as is seen in Case 1, in which the plasma SDHA levels were within a normal range after four and six hours of infusion, did not progressively rise, and had increments upon the initial raised value that were lower than in many normal subjects. Bondy (1958) has recorded a similar instance, and another patient, not referred to here, showed comparable changes in urinary steroids. The duration of plasma SDHA change was unknown, but in normal subjects raised plasma levels return to a normal range shortly after the infusion is stopped (Bayliss and Steinbeck, 1953). One patient (Case 7) did not develop a progressive rise in plasma levels after corticotrophin, although individual values were characteristically high. In the one patient with carcinoma who was tested, corticotrophin did not alter the plasma steroid levels, a feature noted before (Lindsay *et alii*, 1956). In the patient with a moderate-sized adenoma (Case 12; Figure V) plasma SDHA levels rose progressively during the infusion, an occurrence observed before (Lindsay *et alii*, 1956); but the increment of plasma concentrations was within normal limits, although the initial value was raised. In general, these findings are equivalent to those of Soffer *et alii* (1957) obtained by a different technique of corticotrophin stimulation. Post-operatively, in Case 12, the remaining adrenal cortex did not respond to exogenous corticotrophin. Pre-operatively, " SU 4885 " (Ciba), an 11β-hydroxylase inhibitor (Liddle *et alii*, 1959; Gold *et alii*, 1960) was given by mouth, 1 gramme every four hours to a total of 6 grammes in 24 hours, with reduction of the plasma SDHA levels to one-third of their initial value. This suggested endogenous corticotrophin failure as, presumably, it was the adrenocortical adenoma and/or cortex from which it arose that responded to exogenous corticotrophin. In this regard, suppression of endogenous corticotrophin secretion is known to be profound in some instances of the syndrome (Kyle *et alii*, 1957). Although the cortex from which the adenoma arose was greatly compressed, its functional integrity could not be excluded, but was doubtful, because the remaining gland failed to respond to corticotrophin, and both cortices were likely to atrophy from similar factors. Thus, if it is assumed that the endogenous and exogenous forms of corticotrophin have an identical action, it is probable that the adenoma itself was corticotrophin-responsive with a basal secretion that was significantly autonomous, as there appeared to be little endogenous secretion of corticotrophin. In addition, its secretion could be reduced by an 11β-hydroxylase inhibitor.

One patient (Case 4) showed a typical response of adrenocortical hyperplasia to corticotrophin before adrenalectomy; eight months after subtotal adrenalectomy the response was subnormal; nevertheless, this patient had a subsequent recurrence of the syndrome (Bayliss, 1959). In Case 44, the features of hypercorticism were present before operation, and the response to corticotrophin was minimal after subtotal adrenalectomy. Hypocorticism was present, but the remnant was secreting maximally and maintaining normal resting plasma SDHA levels, as in cases of partial

Addison's disease (Steinbeck, 1959); this result is different from the post-operative result in Case 12, which represents total failure of response as in classical Addison's disease and, occasionally, secondary hypocorticism. Thus, as in Addison's disease, normal plasma SDHA levels after adrenalectomy do not exclude hypocorticism. Nevertheless, a low value after adrenalectomy that suggests partial hypocorticism may subsequently improve (Montgomery and Welbourn, 1957). However, it seems likely that low plasma SDHA values obtained by isolated determination will represent hypocorticism.

*Withdrawal Symptoms Following Adrenalectomy.*—Withdrawal symptoms arise in varying measure in most cases, but their seeming persistence after a subtotal procedure should suggest atrophy within the remnant. In this regard, it has seemed that adrenocortical deficiency symptoms are too easily equated with withdrawal symptoms. One patient of the present series and another not included both developed weakness and minor pigmentation soon after operation. These persisted, and continued to be regarded elsewhere as withdrawal features; in both cases steroid replacement was delayed, with prolonged invalidity, and in the latter, pigmentation became intense and has not receded with cortisone. In both cases an early corticotrophin test might have precluded this course. However, an adequate increase in plasma SDHA levels after corticotrophin has been given only shows the presence of adrenocortical tissue capable of responding to this stimulus. As in hypopituitarism, this response may persist although endogenous corticotrophin secretion is depressed (Steinbeck, 1959). Kyle *et alii* (1957) have reported such an instance after Cushing's syndrome, and Liddle *et alii* (1959) have also referred to this problem in testing pituitary reserve.

*The Diagnosis of Cushing's Syndrome with Reference to Plasma SDHA Levels.*—These investigations are based upon semantically acceptable instances of the syndrome, and so the results either confirm the diagnosis or show the variation within the syndrome, rather than indicate the development or limits of the condition. High plasma SDHA levels and their greater than normal increase after corticotrophin suggest adrenocortical hyperplasia, although initial levels may be normal in some cases. If initial levels are raised, the response to corticotrophin infusion may be absent, as in carcinoma and less than normal even in hyperplasia, and may approach normal in adenoma. Thus, the interpretation of plasma SDHA levels is not straightforward. Also, the concentration may be increased by the patient's irritation or unrest and distress from pain, factors which need to be excluded before a raised value is equated with Cushing's syndrome, particularly when the patient is obese and hirsute with a rubicund complexion. A corticotrophin infusion may produce changes in plasma SDHA levels similar to those in Cushing's syndrome, in some patients who have suffered prolonged pain and in some cases of acromegaly (unpublished results); but it is unlikely that these conditions would clinically simulate Cushing's syndrome.

Isolated plasma SDHA determinations can aid the early differential diagnosis of the syndrome, and details of 10 selected cases are shown for illustration in Table VI. These patients were referred by experienced clinicians with the diagnosis of possible Cushing's syndrome. Prior to the SDHA estimation, the results of laboratory tests were interpreted as suggestive evidence for the diagnosis. After SDHA values became available, the original observers had evidence against their original diagnosis, or reconsidered it, or subsequently investigated their patients to confirm that the clinical features were not those of the syndrome. Mostly, the estimation reduced investigations; one clinician discarded the SDHA value, and the patient had an adrenalectomy, without regression of her clinical features. Most of the patients complained of fatigue and weakness, obesity and a changed appearance; most thought that their face was rounder, perhaps more flushed, but only one (Case 34) complained of a red colour, for which there was another cause. Psychological symptoms were frequent, but querulousness rather than irritability predominated. The females had hirsutism of varying degrees, and the pre-menopausal ones menstrual irregularities; impotence in two males appeared psychological; any osteoporosis was difficult to evaluate. Normal SDHA concentrations were considered to exclude the diagnosis; in one case (33) a second estimation was required to establish a stress response. In some cases a normal response to corticotrophin confirmed the value of the isolated estimation, and this would seem a necessary precaution because of apparently normal values in the syndrome. However, some patients subjected to a difficult venepuncture, by repeated attempts, will produce high plasma SDHA levels, and their SDHA value at the start of a corticotrophin infusion may thus be raised; in these, estimation of the urinary steroid excretion before and after corticotrophin may be required to confirm the interpretation of plasma SDHA values.

For instance, a girl, aged 19 years (Case 38), was referred for differential diagnosis. She complained of weight gain, depression, hirsutism and irregular and delayed menstruation; she was obese, with a rounded, flushed face, and had red striæ on the trunk, extending on to the thighs and breasts. Her arterial blood pressure was 160/100 mm. Hg, and she had glycosuria. Her resting plasma SDHA level was 24·9 μg. per 100 ml., and after six hours of corticotrophin infusion became 41 μg.; this increment in concentration was normal, the initial level was raised, and a stress response could not be excluded, nor could it be on subsequent venepunctures because of their difficulty. Finally, urinary steroid values made the presumptive diagnosis unlikely.

Although differential diagnosis has its difficulties, the semantic placing of other patients can be equally difficult on the basis of plasma SDHA levels alone.

Two patients (Cases 39 and 40) were obese females, with a heavy body and thinned legs, and had mooned faces and old stretch marks on the trunk. Both had reduced menstruation, and were hirsute with frontal recession of the scalp hair (to baldness in one) and shaved regularly; they were androgenized, but not virilized. Their glucose tolerance was doubtfully impaired; one was mildly hypertensive, the other not. In both, plasma SDHA levels were normal before and after infusion of corticotrophin, as were the excretions of urinary steroids in Case 40. However, some of these values were at the upper limits of normal, and this patient said that she had had a " high " facial colouring as a younger woman and had received previous " treatment for blood pressure ", and that " sugar " had been found in her urine. These features were no longer present, but old photographs confirmed changes in her facial appearance; also, at laparotomy, her ovaries had a thickened capsule, and contained small cysts and abnormal thecal cells.

These changes suggest an association with hyperfunction of the adrenal cortex (Birke *et alii*, 1956; Perloff *et alii*, 1958). Nevertheless, the full diagnosis in these two cases and in that of the girl, aged 19 years, is doubtful.

In Cases 41 and 42 the patients had some suggestive features of Cushing's syndrome—obesity and rounding of the face and hirsutism with irregular menstruation, and hypertension was significant in one (Case 42) but doubtful in the other, who had radiologically evident osteoporosis and complained of backache. They were 10 to 12 weeks pregnant, and thus the elevated plasma SDHA levels might not be convincing evidence of the syndrome (Bayliss *et alii*, 1953), nor the greater-than-normal increase in these levels after corticotrophin, as in Case 41 (Christy *et alii*, 1955; Cohen *et alii*, 1958). This patient continues to be obese after pregnancy and has progressive hirsutism, but does not fit the context of the syndrome; the other has been accepted elsewhere as an instance of the syndrome.

In Cases 43 and 44 the patients were mildly overweight and hirsute, with long periods of amenorrhœa; neither had a rounded face, although the face was suffused in Case 44. The patients' skin was thickened, and both had emotional disturbances but, although androgenized, were not virilized; one (Case 44) had mild hypertension, the other labile blood pressure. Neither had the familial appearance of Cushing's syndrome. At laparotomy, both had abnormal ovaries, with thickened capsules, many cysts and abnormal thecal cells, these occurring in clusters within the stroma in one (Case 43). In both patients the rise in plasma SDHA levels after corticotrophin infusion was similar to that in Cushing's syndrome due to adrenocortical hyperplasia, the initial values being respectively at the upper limit of normal and raised. The urinary SDHA excretions were not those of the syndrome and there was a plasma-urine dissociation, but the excretions of other steroid groups suggested adrenocortical hyperfunction. One patient (Case 44) had a firm, somewhat nodular, adrenal gland and an atrophic gland at operation, and her post-operative changes in appearance supported the pre-operative suggestion of hypercorticism. The other patient, who was stated to have firm adrenal glands on operative palpation, would not accept further surgery. Because of the history, the isolated SDHA value in Case 45 can neither exclude nor confirm the diagnosis, nor can can it establish a decreased severity of the syndrome, as suggested elsewhere, but requires further elaboration.

*Diagnosis of the Syndrome and Treatment*

Diagnosis of the syndrome must perforce be followed by its surgical correction; therefore, diagnosis cannot lightly be considered and held. In classical instances, plasma SDHA levels merely confirm the need for adrenalectomy, in doubtful cases their estimation should prevent this, when their inherent limitations are appreciated. However, it seems unlikely that this method can be used in borderline cases to decide whether an adrenal process has started that will inevitably result in clinical Cushing's syndrome. Perhaps serial testing with corticotrophin might do so, if serial results progress toward its pattern. In general, if changes in plasma SDHA levels are not convincingly abnormal and the clinical picture is not adequately suggestive of the syndrome, confident equation of plasma SDHA variations with Cushing's syndrome is unlikely unless there is other evidence. Also, plasma SDHA values have inherent difficulties in their inter-

pretation, although Christy *et alii* (1955) thought them more helpful, under some conditions, than the urinary values. One difficulty relates to the delineation of an accepted normal range for the results of corticotrophin stimulation. It is possible that a borderline result obtained by the present method, if associated with a failure to demonstrate a diurnal variation (Doe *et alii*, 1960), would confirm a suggested diagnosis in such cases.

From the cases studied, it is difficult to draw conclusions as to the best form of adrenalectomy for hyperplasia. However, it has seemed that patients subjected to total adrenalectomy have been best managed, for there has been no doubt as to the adrenal status after operation. In this way, post-operative symptoms have been assessed more clearly and treated more confidently, and, perhaps not irrelevantly, when patients live at some distance in the country (as in Case 1), medical directions to the patient have been straightforward. However, after the total procedure there is a definite incidence of pituitary tumours (Nelson and Meakin, 1959; Salassa *et alii*, 1959; Nelson *et alii*, 1960; Ray, 1960) and the patient is always totally dependent upon replacement therapy, and some authors prefer the subtotal procedure (Cope and Raker, 1955; Mason, 1957; Montgomery and Welbourn, 1957). After subtotal adrenalectomy management has seemed less certain, and on occasions replacement therapy has been withheld because of assumed integrity of the adrenal remnant or a desire to prevent its atrophy. This has produced prolonged hypocorticism and invalidity in some cases, and in one definite personality changes (Cleghorn, 1953). Also, the subtotal procedure carries a variously assessed risk of recurrence (Sprague, 1953; Mason, 1957). In addition, the number of patients requiring final replacement therapy in the series of Montgomery and Welbourn (1957), the need for a radical procedure to induce adequate regression of the syndrome (Sprague, 1953) and the unknown quantity of survival of the adrenal remnant would support total adrenalectomy as the procedure of choice (Glenn *et alii*, 1958).

## ACKNOWLEDGEMENTS

I am particularly indebted to Dr. R. I. S. Bayliss for his original interest and unfailing support in this investigation, to the physicians and surgeons who referred patients for study, to Mr. H. H. Knop of Ciba Co. Pty. Ltd. (Pharmaceutical Division) for a ready gift of "SU-4885", and to Dr. J. B. Cope for his constant help in many ways.

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# FIBRINOLYSIS, BLOOD CLOTTING, SERUM LIPIDS AND BODY BUILD IN NATIVES OF NEW GUINEA AND AUSTRALIANS[1]

R. B. GOLDRICK[2]

*From the Clinical Research Department, Kanematsu Institute, Sydney Hospital, Sydney*

SUMMARY

Measurements of height, weight, body bulk and fatness (skinfold thickness) and of serum lipids and fibrinolytic activity of fasting blood, were made in three groups of males—40 healthy Australians, aged 25 years, 35 atherosclerotic Australians, aged 60 years, and 40 healthy natives, aged 25 years. Measurements of the " Stypven " clotting time were also made in the Australians and compared with previous observations among the natives.

The atherosclerotic group had the highest concentrations of serum cholesterol, phospholipid and beta lipoprotein cholesterol (paper electrophoresis and cholesterol elution), and the lowest serum P/C ratio. The concentration of alpha lipoprotein cholesterol was highest in the healthy Australians and lowest in the natives, while the serum P/C ratio was higher, and the serum cholesterol lower, in the natives than in the healthy Australians.

Ultracentrifugal studies revealed that the higher serum P/C ratio in the natives was due to their high-density lipoprotein, which carried as much phospholipid as, but less cholesterol than, the corresponding fraction in healthy Australians. Increasing fatness among young Australians was associated with a decrease in alpha and an increase in beta lipoprotein cholesterol.

Clotting times differed significantly in all groups, being longest in the healthy Australians and shortest in the natives. Alpha lipoprotein was associated with prolongation of clotting in the " Stypven " test.

Fibrinolytic activity was similar in both groups of Australians, but was greatly increased in the natives. Slowing of the rate of fibrinolysis was associated with increasing body fatness and body bulk in the Australians. In the natives muscle, not fat was the major contributor to body bulk, and increasing body bulk was associated with an acceleration of fibrinolysis.

The results are discussed especially in regard to the thrombogenic and lipid theories of atherogenesis.

## INTRODUCTION

BLOOD clots more quickly in the native men of New Guinea than in Australians, yet the latter possess higher serum concentrations of cholesterol and beta lipoprotein, and are fatter and more prone to atherosclerosis and coronary heart disease (Goldrick and Whyte, 1959). Not only was this difference in blood coagulability surprising, but it was also at variance with the report by McDonald and Edgill (1957) that blood clotting is more rapid in atherosclerotic individuals than in healthy controls.

The present investigation was undertaken to extend the study of blood coagulability and to determine fibrinolytic activity in natives of New Guinea, and in healthy and atherosclerotic Australians. It seemed likely that if the tendency to form fibrin is of any importance in regard to atherogenesis—and the reports of Duguid (1946, 1948), McDonald and Edgill (1957) and Morgan (1956) indicate that it is—then the faster rate of clotting in the natives might be compensated for by a more rapid rate of fibrinolysis than in Australians.

Measurements of body build and serum lipids and lipoproteins were also made, in order to confirm the relationships between rate of blood clotting and alpha lipoprotein and between body fatness and the lipoprotein distribution of cholesterol, which have been noted in earlier reports (Goldrick and Whyte, 1959; Goldrick, 1960), and which seem pertinent to atherogenesis. It was also hoped to determine whether the rate of fibrinolysis was associated with any of these factors.

## MATERIALS AND METHODS

### SUBJECTS

The Australian subjects comprised 40 healthy male resident medical officers and 35 men with unequivocal evidence of atherosclerotic complications—namely, myocardial infarction, angina

[1] Received on June 20, 1960.

[2] This work was supported by an Anonymous Family Trust.

pectoris or peripheral vascular disease. The ages ranged from 22 to 31 years, averaging 25 years, in the healthy men, and from 40 to 72, averaging 60 years, in the atherosclerotics. None of the subjects in the atherosclerotic group had experienced thrombotic episodes within six months of examination. Dietary fat provided about 38% of the caloric intake of both groups of subjects.

Forty native labourers living at Goroka in the Central Highlands of New Guinea were selected after a full physical examination had revealed no abnormalities. Their ages ranged from 13 to 40 years, averaging 25 years. Dietary fat had provided only up to 5% of their total caloric intake when they were leading an ordinary village life; but these subjects had been consuming Government rations for an average of two and a half years. This meant that their consumption of protein and fat had increased, so that fat provided about 18% of the total caloric intake.

Measurements of blood coagulation were not made in the present group of natives, but the results of observations made previously in the same district have been drawn upon (Goldrick and Whyte, 1959).

### *Collection and Analysis of Blood*

All blood samples were collected by clean venepuncture with subjects in the fasting state. Only limited exercise had been undertaken prior to bleeding, and all venepunctures were performed between the hours of 8 and 9 a.m.

Fibrinolytic activity was determined on whole blood by the method of Fearnley *et alii* (1957). The standard deviation of the differences between duplicates was 1·47 hours, derived from the expression

$$\sigma_e = \sqrt{\frac{\Sigma d^2}{2n}}.$$

Measurements of serum total cholesterol, phospholipid and alpha and beta lipoprotein cholesterol (paper electrophoresis and cholesterol elution) and the "Stypven" clotting time were performed in duplicate by methods described elsewhere (Goldrick and Whyte, 1959).

High-density and low-density lipoproteins were isolated by the method of Havel *et alii* (1955). The relative density of 5 ml. of serum was adjusted to 1·063, and the lipoprotein fractions were separated by centrifugation for 22 hours in the 40·3 rotor of a model L "Spinco" preparative ultracentrifuge at an average of 114,400×G. After separation, each of the lipoprotein fractions was made up to 15 ml. with distilled water, and its cholesterol and phospholipid concentrations were measured. Recovery of cholesterol averaged 95% of the total in the natives and 70% in the healthy Australians. The poor recovery of lipid in the Australians was confined to low-density lipoprotein, and can be attributed to early difficulties in cutting the "Lusteroid" centrifuge tubes. After the tube cutter was modified, good recovery was obtained. This loss of lipid is unlikely to have detracted from the validity of the P/C ratio, but it has prevented a comparison being made of the absolute values of the cholesterol and phospholipid content of low density lipoprotein found in the different groups of subjects.

### *Body Build*

Body weight was measured to the nearest pound and height to the nearest inch. Body fatness was taken as the sum in millimetres of the skinfold thicknesses measured at three sites (over the right triceps, under the angle of the right scapula and one inch to the right of the umbilicus) by means of spring calipers. An estimate of body bulk relative to height was derived from the expression $\frac{\text{Weight}}{(\text{Height})^2} \times 1000$.

## RESULTS

### DIFFERENCES BETWEEN THE GROUPS OF SUBJECTS

### *Body Build*

The average values for body weight, height, fatness (skinfold thicknesses) and body bulk in relation to height are given in Table I. Both groups of Australians were obviously taller, heavier and fatter than the natives, but body bulk, when allowance was made for differences in height, was the same. This implies that the Australians had relatively less muscle and more fat than the natives. Heredity and

TABLE I

*A Comparison, Giving the Mean Values, Standard Deviations and Significance of the Differences of the Bodily Characteristics of Healthy and Atherosclerotic Australians and Natives of New Guinea*

| Characteristic | Healthy Australians (40) | Atherosclerotic Australians (35) | Natives (40) | Significance of Difference (*P*) | | |
|---|---|---|---|---|---|---|
| | | | | Healthy Australians versus Atherosclerotics | Healthy Australians versus Natives | Atherosclerotics versus Natives |
| Height (inches) .. .. | 70·04± 2·50 | 67·34± 2·39 | 63·25± 2·21 | <0·001 | <0·001 | <0·001 |
| Weight (pounds) .. .. | 165·28±17·81 | 136·31±24·47 | 131·9 ±12·42 | — | <0·001 | <0·001 |
| Weight/Height²×1000 .. | 33·714± 3·476 | 34·331± 4·140 | 32·910± 2·066 | — | — | — |
| Sum of skinfold thicknesses (millimetres) .. .. | 52·40±23·47 | 50·29±20·21 | 28·38± 7·39 | — | <0·001 | <0·001 |

differences in diet, diseases and physical activity were probably responsible for this. The indices of body build were similar among the two groups of Australians, except that height was greater in the healthy controls.

### *Serum Lipids*

There were significant differences in the serum lipids and lipoproteins between the groups (Table II). The serum cholesterol level was highest in the atherosclerotic subjects and lowest in the natives, with the healthy Australians occupying an intermediate position. Phospholipid and beta lipoprotein cholesterol levels were similar among the natives and healthy Australians, while higher values were recorded in the atherosclerotics. All the groups differed in regard to the serum concentration of alpha lipoprotein cholesterol, which was highest in the healthy Australians and lowest in the natives. The percentage of the total cholesterol carried in beta lipoprotein was similar in atherosclerotics and natives, but was greater in these subjects than in the healthy Australians. The P/C ratio of serum differed among the subjects, being highest in the natives and lowest in the atherosclerotics. It will be noted that the P/C ratio of high density lipoprotein was higher in the natives than in the healthy Australians, while the P/C ratios of low density lipoprotein were similar. Hence the higher serum P/C ratio in natives compared with healthy Australians is accounted for by the difference in composition of high density lipoprotein.

### *Blood Clotting*

The rate of blood clotting differed significantly between the various groups (Table III). The "Stypven" time in healthy Australians (68·28 seconds) was longer than in atherosclerotics (61·77 seconds; $P<0·05$), and clotting times in both these groups were longer than in the natives (41·4 seconds; $P<0·001$).

### *Fibrinolysis Time*

The natives were able to dissolve their clots much more rapidly than the Australians (Table III). The fibrinolysis times were similar in the two groups of Australians, averaging 10·58 hours in the healthy controls and 8·11 hours in the atherosclerotic subjects. The fibrinolysis time of 3·06 hours in the natives was significantly shorter than in both the healthy and the atherosclerotic Australians ($P<0·01$ and $P<0·001$ respectively).

## INTERRELATIONSHIPS BETWEEN SERUM LIPIDS, BLOOD CLOTTING, FIBRINOLYSIS TIME AND BODY BUILD

The data from the three groups of subjects were further analysed to determine whether any significant interrelationships existed between the various lipids, the results of the blood clotting and fibrinolysis tests and the indices of body build.

### *Fibrinolysis Time*

*Healthy Australians.*—There was no relationship between the rate of clot lysis and total cholesterol, phospholipid, alpha and beta lipo-

TABLE II

*Serum Lipid Values in Healthy and Atherosclerotic Australians and in Natives of New Guinea*

| Serum Lipids | Healthy Australians (40) | Atherosclerotic Australians (35) | Natives (40) | Significance of Difference ($P$) | | |
|---|---|---|---|---|---|---|
| | | | | Healthy Australians versus Atherosclerotics | Healthy Australians versus Natives | Atherosclerotics versus Natives |
| Total cholesterol (milligrammes/100 millilitres) .. | 218·6 ±42·13 | 273·5 ±54·95 | 192·3 ±44·90 | <0·001 | <0·01 | <0·001 |
| Total phospholipids (milligrammes/100 millilitres) .. | 238·2 ±33·75 | 276·7 ±39·72 | 231·5 ±40·07 | <0·001 | — | <0·001 |
| Alpha lipoprotein cholesterol (milligrammes/100 millilitres) | 39·7 ±10·35 | 34·6 ±11·13 | 22·8 ± 5·82 | <0·05 | <0·001 | <0·001 |
| Beta lipoprotein cholesterol (milligrammes/100 millilitres) | 179·6 ±26·54 | 239·3 ±55·13 | 169·5 ±43·52 | <0·001 | — | <0·001 |
| Serum phospholipid/cholesterol ratio .. .. .. | 1·1043± 0·1088 | 1·0299± 0·1199 | 1·2213± 0·1136 | <0·01 | <0·001 | <0·001 |
| Phospholipid/cholesterol ratio of high density lipoprotein | 2·061± 0·635 | | 2·727± 0·367 | | <0·001 | |
| Phospholipid/cholesterol ratio of low density lipoprotein | 0·847± 0·295 | | 0·869± 0·084 | | — | |
| Beta lipoprotein (percentage of total cholesterol) .. | 81·17 ± 5·50 | 86·99 ± 4·49 | 87·80 ± 3·26 | <0·001 | <0·001 | — |

TABLE III

*The Results of Fibrinolysis and Blood Clotting Tests in Healthy and Atherosclerotic Australians and Natives of New Guinea*

| Characteristic | Healthy Australians (40) | Atherosclerotic Australians (35) | Natives (40) | Significance of Difference ($P$) | | |
|---|---|---|---|---|---|---|
| | | | | Healthy Australians versus Atherosclerotics | Healthy Australians versus Natives | Atherosclerotics versus Natives |
| Fibrinolysis time (hours) .. | 10·58±16·14 | 8·11± 7·94 | 3·06± 1·04 | — | <0·01 | <0·001 |
| "Stypven" clotting time (seconds) .. .. .. | 68·28±15·42 | 61·77±11·09 | 41·4 ± 9·6[1] | <0·05 | <0·001 | <0·001 |

[1] Data drawn from a previous study on a similar group of New Guinea natives.

protein cholesterol, and the P/C ratios of high and low density lipoproteins. However, fibrinolysis time showed evidence of being related to the percentage of total cholesterol in beta lipoprotein ($r=+0·310$; $P<0·05$), body bulk ($r=+0·381$; $P<0·02$) and body fatness ($r=+0·422$; $P<0·01$), indicating that fibrinolytic activity is reduced as the values of these other measures are increased.

The relationship between the percentage of cholesterol in beta lipoprotein and fibrinolysis time was tested again by the use of partial correlation coefficients, and became insignificant when the influence of body fatness was held constant. It is concluded that none of the serum lipids measured has any valid relationship to the rate of clot lysis.

The partial correlation coefficients relating body fatness and bulk to fibrinolysis time (with the influence of the lipoprotein fractions held constant) remained statistically significant ($r$ for fibrinolysis time and fat with alpha and beta cholesterol constant $=+0·357$, $P<0·05$; and $r$ for fibrinolysis time and bulk with alpha and beta cholesterol constant $=0·336$, $P<0·05$), confirming the validity of these associations.

When attempts were made to evaluate separately the relationships of bulk and fatness to clot lysis, difficulties were encountered. Bulk was closely related to fatness ($r=0·813$; $P<0·001$), and the partial correlations ($r$ for fibrinolysis time and fat with bulk constant $=+0·208$ and $r$ for fibrinolysis time and bulk with fat constant $=+0·072$) were not significant, although the partial correlation coefficient for fibrinolysis time and fatness was almost three times as great as that of fibrinolysis time and body bulk. Evidently fatness contributes so much to body bulk in the average over-nourished Australian that these two measures cannot be considered separately.

*Atherosclerotic Australians.*—There were no relationships between the levels of total cholesterol and phospholipid and the rate of clot lysis. However, there were significant associations between fibrinolysis time and bulk ($r=+0·508$; $P<0·001$), fatness ($r=+0·567$; $P<0·001$), alpha cholesterol ($r=-0·340$; $P<0·05$), beta cholesterol ($r=+0·321$; $P<0·05$) and the percentage of total cholesterol in beta lipoprotein ($r=+0·412$; $P<0·02$).

The coefficients relating fibrinolysis time and the lipoprotein fractions were further tested, partial correlations being used, with the influence in turn of fatness and bulk held constant. The partial correlation coefficients were all insignificant, and the correlations between the serum lipoproteins and fibrinolysis time can be discounted as unimportant.

On the other hand, the partial correlation coefficients of bulk and fatness against lysis time retained their significance when the influence of the lipoprotein fractions was held constant ($r$ for fibrinolysis time and fatness with alpha and beta cholesterol constant $=+0·538$, $P<0·001$; $r$ for fibrinolysis time and bulk with alpha and beta cholesterol constant $=+0·472$, $P<0·01$), confirming their validity.

Difficulties were again encountered when attempts were made to evaluate separately the relationships of bulk and fatness to the rate of clot lysis. Bulk was closely related to body fatness ($r=+0·720$; $P<0·001$), and both partial correlation coefficients ($r$ for fibrinolysis time and fatness with bulk constant $=+0·336$, and $r$ for fibrinolysis time and bulk with fatness constant $=+0·175$) were insignificant. In these subjects also, bulk and fatness are really inseparable.

*Natives.*—The fibrinolysis time was inversely correlated with body bulk ($r=-0·364$; $P<0·05$), and as bulk is derived to a large extent from muscle in these people, this relationship suggests that fibrinolytic activity became more marked with increasing muscularity.

There was no association between the lysis time and the serum lipids and lipoproteins and the other indices of body build.

### *"Stypven" Time*

There were significant associations between clotting in the "Stypven" test and alpha lipoprotein cholesterol in the healthy Australians ($r=+0\cdot440$; $P<0\cdot01$) and atherosclerotic Australians ($r=+0\cdot326$; $P<0\cdot05$). The "Stypven" time was also correlated with the percentage of total cholesterol in beta lipoprotein in both groups ($r=-0\cdot494$, $P<0\cdot001$, and $r=-0\cdot388$, $P<0\cdot02$, respectively). In other words, the "Stypven" time became longer as the concentration of alpha lipoprotein increased, and shorter with an increasing percentage of the total cholesterol in beta lipoprotein. These associations confirm the findings of earlier, more detailed studies (Goldrick and Whyte, 1959; Goldrick, 1960).

There was no relationship between the "Stypven" time and the indices of body build in either of these groups of subjects.

The rate of clot lysis bore no relation to the "Stypven" time in either the healthy controls ($r=-0\cdot297$) or the atherosclerosis ($r=-0\cdot237$); moreover, these coefficients were not improved when partial correlations were carried out with the influences of fatness, bulk and the lipoprotein fractions held constant.

### *Body Fatness*

There were significant relationships between skinfold thickness and relative body bulk in both the healthy and the atherosclerotic Australians ($r=+0\cdot813$, $P<0\cdot001$), and $r=+0\cdot720$, $P<0\cdot001$, respectively), but not in the natives ($r=+0\cdot089$), indicating that fat is an important contributor to body bulk only in Australians.

In the healthy Australians body fatness was associated with beta cholesterol ($r=+0\cdot323$; $P<0\cdot05$), and the percentage of total cholesterol carried in beta lipoprotein ($r=+0\cdot412$; $P<0\cdot01$), but not with total cholesterol ($r=+0\cdot244$). Thus, obesity in healthy young Australians bears no relationship to the concentration of the serum total cholesterol, but is associated with a tendency to transport more cholesterol in beta and less in alpha lipoprotein. There were no significant associations between fatness and the "Stypven" time, the serum phospholipid concentration or the P/C ratios of high and low density lipoproteins.

Among the atherosclerotic subjects, fatness bore no relationship to the serum lipids and lipoproteins or to the rate of blood clotting.

Fatness in the natives was associated with the concentration of cholesterol in low density lipoprotein ($r=+0\cdot304$; $P<0\cdot05$), but not with beta lipoprotein cholesterol measured by paper electrophoresis ($r=+0\cdot285$) or with any of the other lipids. In view of the discrepancy in the relationships between skinfold thickness and the cholesterol in beta and low density lipoproteins and the low order of significance of the latter, it is doubtful whether fatness does indeed have any noteworthy association with low density lipoprotein cholesterol in these people.

The relationships between fatness and the rate of fibrinolysis in the various groups of subjects have already been mentioned.

## DISCUSSION

Abnormalities in the serum lipids of individuals manifesting the complications of atherosclerosis, when compared with age-matched controls, are said to be an elevation of the serum cholesterol (Lawry *et alii*, 1957), low serum P/C ratio (Oliver and Boyd, 1953), and reduced alpha lipoprotein with increased beta lipoprotein (Barr *et alii*, 1951; Jenks *et alii*, 1956). Indeed, these are the differences observed among the healthy and atherosclerotic Australians. However, as there is a rise in cholesterol, phospholipid (Adlersberg *et alii*, 1956), and beta lipoprotein (Russ *et alii*, 1951), with advancing age, the differences observed in the Australian subjects are partly attributable to discrepancy in ages.

The group of elderly "atherosclerotic" Australians has been included in this comparison so as to provide as wide a spectrum of atherosclerosis as possible. It is presumed that, by and large, the elderly Australian men suffered a more severe degree of atherosclerosis than did the young Australian men, and that the arteries of the latter were likely to be more severely diseased than those of the natives. The factor of aging is obviously of importance when the data derived from the "atherosclerotic" group are considered, but this has merely been used to exaggerate differences in arterial disease. The present study, then, involves for the most part measurement of various attributes (lipids, clotting, etc.) in three groups of subjects who differed in many respects, one of which was presumably severity of atherosclerosis, and a search for possible correlations between these

attributes and the degree of atherosclerosis. One difficulty inherent in a study of this kind lies in the interpretation of correlations, many of which, while statistically significant, are of a low order of magnitude. Indeed, this is likely to be the case when atherogenesis is considered—a process which is probably influenced by many factors.

The low concentration of serum cholesterol and the high P/C ratio among the natives, in comparison to both groups of Australians, are in accord with earlier experiences in New Guinea (de Wolfe and Whyte, 1958; Goldrick and Whyte, 1959). However, the levels of cholesterol, phospholipid and beta cholesterol are higher, while the serum P/C ratio and the concentration of alpha lipoprotein are lower, in the present group of natives than previously found in these people. The discrepancies are probably of dietary origin, since the natives in this study had been consuming Government rations, which supply additional fat and protein, for an average of two and a half years, while subjects in the earlier reports either had been consuming village diets or had been receiving extra rations for only a short period. The prolonged intake of Government rations supplying 18% of total calories from fat, in contrast to 5% in the village diet, represents a large increase in fat consumption, which may well lead to elevated levels of cholesterol, phospholipid and beta lipoprotein.

The village natives and natives in receipt of dietary supplements for short periods possess lower levels of cholesterol, phospholipid and beta lipoprotein than do age-matched Australians; but all the groups so far studied in New Guinea have exhibited very low levels of alpha lipoprotein cholesterol. With the exception of the latter, their lipid levels are comparable to those observed in other primitive races subsisting on similar diets (Bronte-Stewart *et alii*, 1955; Mann, 1955), and undoubtedly reflect their low intake of dietary fat. However, the tendency among natives to carry little cholesterol in alpha lipoprotein cannot be explained in terms of dietary factors, and the values recorded fall short of the lowermost limit of the normal range in other population groups (Keys *et alii*, 1958).

This unusual mode of cholesterol transport in the native is responsible for his high percentage of total cholesterol in beta lipoprotein, and the combination of the two bears a superficial resemblance to the lipoprotein patterns of atherosclerotics. However, under normal circumstances the concentration of total cholesterol is sufficiently low to enable smaller quantities of cholesterol to be carried in the beta fraction than in Australians. Only when the total cholesterol level is elevated, as in the present group of natives, are the beta cholesterol levels comparable to those found in this country.

The high serum P/C ratio is another reflection of the low concentration of alpha cholesterol. It has been shown that the high P/C ratio of native serum relative to healthy Australian serum is accounted for solely by the high P/C ratio of high-density lipoprotein. The latter in turn is secondary to an absolute decrease in the cholesterol, rather than to an absolute increase in the phospholipid content of high-density lipoprotein (HDL cholesterol of Australians 44·5 mg. per 100 ml., and of natives 34·5 mg. per 100 ml.; $P<0{\cdot}001$: HDL phospholipid of Australians 88 mg. per 100 ml., and of natives 93 mg. per 100 ml.; $P>0{\cdot}05$). In effect, the native of New Guinea possesses, by our standards, a " normal " lipoprotein transport system for phospholipid, but a somewhat unique system for carrying cholesterol.

If it is borne in mind that the lipid levels in the present group of natives are generally higher than those usually found in these people, the results of the various studies in New Guinea and Australia may be interpreted as supportive evidence for the filtration hypothesis of atherogenesis (Page, 1954). According to this view, high concentrations of beta lipoprotein and low P/C ratios are indicative of an acceleration of the atherosclerotic process. This would be considered as most marked in the atherosclerotic Australians, less so in the healthy Australians, and least evident in the natives, and the serum lipid patterns would correlate with the degree of atherosclerosis which we presume to exist in the three groups of subjects.

If the results of the measures of blood clotting and fibrinolytic activity truly reflect conditions *in vivo*, it would appear that elderly atherosclerotic Australians differ from young healthy Australians, not in their ability to dissolve fibrin, but to some extent in their tending to form it more rapidly. McDonald and Edgill (1957) have also reported a hypercoagulable state in atherosclerotic subjects in comparison to age-matched controls, although this has been denied by others (Merskey *et alii*, 1958).

The natives of New Guinea differ from healthy and atherosclerotic Australians in forming and dissolving fibrin more rapidly, but the tendency of their blood to clot quickly is more than outweighed by their very rapid rates of fibrinolysis. As is shown by the data in Table III, clotting occurs about one and a half times faster, while the dissolution of clots occurs some

three times faster, in natives than in Australians. If we concede that the tendency to deposit fibrin is the resultant of two opposing processes—fibrin formation and fibrinolysis—then the overall tendency among natives to deposit fibrin is conceivably less pronounced than in Australians. Merskey *et alii* (1958) have undertaken similar studies on the Bantus of South Africa, who, like the natives of New Guinea, are relatively free from atherosclerosis and its complications (Higginson and Pepler, 1954; Vogelpoel and Schrire, 1955). They found a greater degree of fibrinolytic activity in the Bantus than in healthy and atherosclerotic Europeans, but no difference in blood clotting.

This study suggests a relationship of blood coagulability (viewed from both aspects, clotting and fibrinolysis) to the severity of atherosclerosis and the tendency to develop its complications. However, more confirmatory evidence must be forthcoming before this relationship can be accepted as holding true in all population groups. Consideration must also be given to the possibility that the hypercoagulable state in atherosclerotic individuals is the result rather than the cause of their disease; but this seems unlikely in view of the greater tendency to fibrin deposition in apparently healthy Europeans than in primitive races relatively immune to severe atherosclerosis and its sequelæ. If its limitations are borne in mind, the evidence suggesting that generalized states of hypercoagulability are to be found in men with the clinical manifestations of atherosclerosis and to a lesser degree in men predisposed to these conditions is in full accord with Duguid's (1946, 1948) contentions that thrombosis is a primary factor in atherogenesis and not merely secondary to established intimal disease.

If we assume that lipid filtration and fibrin deposition are of importance in the atherosclerotic process, the relationship between alpha lipoprotein and prolongation of clotting in the "Stypven" test acquires some significance. This relationship has been observed in both the healthy and atherosclerotic Australians in the present study, and in similar subjects when the serum lipids in the fasting state were forced to change (Goldrick, 1960). It has also been found in natives of New Guinea (Goldrick and Whyte, 1959). Thus there can be no doubt about the validity of the association, but its interpretation is uncertain. It remains to be seen whether alpha lipoprotein itself is able to inhibit clotting, or whether it is some closely related non-lipoprotein factor. Nevertheless, a low concentration of alpha lipoprotein is characteristic of atherosclerotic disease, and is associated with a shorter clotting time and an increased liability to thrombosis. It is not unlikely that some lipid constituent of alpha lipoprotein may influence blood coagulation, just as do certain lipids appearing in the circulation during alimentary lipæmia (Poole, 1958). Thus, fibrin deposition and lipid filtration may be associated phenomena. Fibrinolysis is said to be inhibited during alimentary lipæmia (Greig, 1956), but the results of the present study give no suggestion that the serum lipids in the fasting state are of any importance in this respect.

People who are overweight experience an excessive mortality from a number of disorders, one of which is ischæmic heart disease (Dublin and Marks, 1951), and it is interesting to examine the present results for any lipid or thrombotic factors which might possibly account for this relationship. Positive clues are to be found in each of the three groups of subjects. Among the natives, gross obesity is almost unknown and variations in the thickness of their subcutaneous fat are not related to variations in body bulk. Muscle, rather than fat, is the major variable tissue, and increasing muscularity, through its contribution to body bulk, is associated with an acceleration of fibrinolysis. However, there is variation in the amount of fat to be found, and increasing fatness is related to a shortening of the "Stypven" time (Goldrick and Whyte, 1959), but not to changes in the serum lipids or to the rate of clot lysis. In Australians, on the other hand, obesity contributes significantly to differences observed in body bulk, and increasing degrees of fatness are associated with reduced fibrinolytic activity and, in young Australians, with diminished amounts of alpha and increased amounts of beta lipoprotein. Obesity is also associated with increased blood pressure, by virtue of the increased bulk of the body (Whyte, 1959), and this provides an additional factor favouring lipid filtration.

As it seems highly improbable that the amounts of fat and muscle in the body are directly responsible for changes in blood pressure, serum lipids, blood clotting and fibrinolysis, it is evident that other factors are involved in producing these relationships. The bulk of an individual and the relative contributions to bulk from muscle and fat are the expressions of the interaction of a number of factors, of which diet (total calories and the caloric contributions from fat, protein and carbohydrate), physical activity, sex hormones and genetic factors would seem to be the most important. Consequently, the relationships of body build to blood pressure, serum lipids, blood clotting and fibrinolysis must also involve these other factors which determine body build. In other words, the interaction of diet, physical activity,

and so on, which we measure as obesity or muscularity or simply as bulk, is associated with changes in blood pressure, serum lipids, blood clotting and fibrinolysis. On this basis, one would anticipate the relationships of body build to blood pressure, serum lipids, etc., to differ in peoples whose diets, exercise patterns and genetic constitutions are dissimilar; and on reference to the correlations, this would seem to be the case. Indeed, knowledge of the factors responsible for the accretion of fat and muscle in the individual may be of greater importance than measuring his degree of muscularity and obesity.

It is of interest that the incidence of ischæmic heart disease is high in those who consume diets rich in fats (Keys and White, 1956; Jolliffe, 1959), are physically inactive (Morris *et alii*, 1953; Morris and Crawford, 1958), are of the male sex (Ryle and Russell, 1949), and are members of certain families (Adlersberg *et alii*, 1949; Epstein *et alii*, 1959). It is also noteworthy that diet (Ahrens, 1957), physical activity (Mann *et alii*, 1955), sex hormones (Oliver and Boyd, 1956), and genetic factors (Schaefer *et alii*, 1958*a*, 1958*b*), influence the levels of the serum lipids, and consequently some or all of these factors may in some way affect blood pressure, blood clotting or fibrinolysis. If this is so, then it is possible that factors in our mode of living and genetic constitution which determine susceptibility to ischæmic heart disease might influence atherogenesis by facilitating lipid filtration and fibrin deposition.

## ACKNOWLEDGEMENTS

The expenses of this investigation were met by an Anonymous Family Trust. The writer is grateful for the willing cooperation of Dr. R. F. J. Scragg, Director of Public Health in Papua and New Guinea, and to Dr. J. Kariks and his staff in Goroka and to the medical staff of Sydney Hospital for their interest and assistance. It is a pleasure to thank Dr. H. M. Whyte for his advice and encouragement and Mr. J. Panter for his technical assistance.

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# OBSERVATIONS ON HEPARIN–INDUCED CLEARING ACTIVITY IN ISCHÆMIC HEART DISEASE AND THE EFFECT OF PROLONGED HEPARIN THERAPY[1]

P. J. NESTEL[2]

*From the University of Melbourne Department of Medicine, Royal Melbourne Hospital*

SUMMARY

Inhibition of heparin-induced plasma-clearing activity has been compared in patients with ischæmic heart disease and age-matched control subjects. It has been found that the increased inhibitory activity of the plasma of patients with ischæmic heart disease was due to increased inhibitor activity associated with the patients' blood platelets. The inhibitory activities of platelet-poor plasma were similar in the two groups.

It has also been found that heparin-induced clearing activity was low one month after a myocardial infarction, but increased gradually over the next seven months.

The effect of prolonged intermittent heparin therapy on heparin-induced clearing activity has been studied over a period of seven months in a group of patients who had survived a myocardial infarction. The mean increase in clearing activity was significantly greater in this treated group than in a closely matched group of patients who were not being treated.

IN patients with ischæmic heart disease, abnormalities of lipid metabolism have been frequently described. Such patients differ from healthy subjects in developing an abnormally intense alimentary lipæmia (Bronte-Stewart and Blackburn, 1958), which is cleared poorly by injections of heparin (Oliver and Boyd, 1953). These findings have suggested an abnormality in the heparin-induced clearing system, an enzyme system which is partly responsible for the physiological disposal of fat (Havel and Fredrickson, 1956). Using an in-vitro technique, Nestel and Mashford (1960) showed that, after an injection of heparin, the plasma of patients with ischæmic heart disease contained on the average less clearing activity than the plasma of control subjects, provided that the plasmas were rich in platelets. It was also found that the patients' platelet-rich plasma, obtained without a prior injection of heparin, inhibited a standard source of clearing factor more than did the plasma of the controls. Although it seemed probable that the differences found were due to the presence of increased inhibitor activity associated with the platelets of the ischæmic group, it was not certain whether the inhibitor activity of platelet-poor plasma might also contribute to the differences. In the present paper, the inhibitor activities of platelet-rich plasma, platelet extracts and platelet-poor plasma are compared in patients with ischæmic heart disease and in normal controls.

Nestel and Mashford (1960) also showed that a small group of patients who had been receiving injections of heparin twice a week for at least four months after a myocardial infarction showed as much clearing activity in their post-heparin plasma as did the controls. This observation was made in a retrospective study of patients who had been receiving heparin for varying periods of time ranging from four to nine months. A prospective study has now been made, in which the effects of long-term heparin therapy on the clearing activity of post-heparin plasma of a group of patients with ischæmic heart disease has been compared with the findings in another group of similar patients who were not receiving heparin twice a week. The results of this study are also presented in this paper.

## MATERIAL AND METHODS

### *Inhibitor Activity of Platelet-Rich Plasma and Platelet Extracts in Ischæmic Heart Disease*

Two groups of male subjects who were closely matched for age (mean ages being 51 and 54 years) were investigated. Group I, the controls, comprised 11 healthy hospital employees; Group II, 11 patients, had suffered a transmural myocardial infarction at least three months previously. The patients were in good health at the time of the investigation and were not being treated.

[1] Received on September 2, 1960.

[2] Assistant to Professor R. R. H. Lovell, Professor of Medicine.

Observations were made after an overnight fast. Blood was collected with siliconed glassware and stored in siliconed iced tubes. EDTA solution (1%) was used as anticoagulant. The blood was spun at 4° C. at 1000 r.p.m. for 15 minutes to obtain platelet-rich plasma. Platelet extracts were prepared from duplicate samples of platelet-rich plasma, which were spun again at 3000 r.p.m. for 15 minutes. The supernatant platelet-poor plasma was discarded. The plug of platelets was homogenized with a glass rod, and the homogenate was resuspended in a volume of buffered saline equivalent to that of the original plasma. After further rapid centrifugation, the supernatant extract was retained and the platelet débris discarded.

Inhibitor activity was measured in aliquots of platelet-rich plasma and platelet extract obtained from all subjects in the two groups. To one-millilitre aliquots of each was added 1 ml. of a standard source of plasma containing clearing factor (which was obtained by bleeding a young donor eight minutes after an intravenous injection of 3 mg. of heparin); 0·2 ml. of a 0·5% coconut-oil emulsion ("Ediol") was then added as substrate, and the mixture was incubated at 30° C. Measurements of the fall in optical density of the mixture were made every 10 minutes for 60 minutes in a "Unicam" spectrophotometer. The fall in optical density at the end of one hour provided a measure of inhibition exerted by platelet-rich plasma or platelet extract upon the clearing activity of the standard post-heparin plasma, since the fall in optical density is inversely related to inhibitory activity.

### *Effect on Heparin-Induced Clearing Activity of Long-Term Heparin Therapy*

Twenty male patients who had recovered from a transmural myocardial infarction were selected for study. They were divided into two equal groups closely matched for age (the mean ages of the two groups being 55 and 56 years) and severity of illness. Four weeks after the infarction, when all the patients had been discharged from hospital, one group were given daily placebo tablets and the other group a twice-weekly subcutaneous injection of 250 mg. of aqueous heparin solution. Heparin-induced clearing activity was measured in each subject at the beginning of treatment and about four and seven months later. Since it was found that stimulation of clearing activity by 250 mg. of heparin administered subcutaneously did not last longer than 72 hours, blood for study was obtained from the heparin-treated group four days after their previous injection. Clearing activity was measured in platelet-rich plasma, which was obtained eight minutes after an intravenous injection of 3 mg. of heparin. The falls in optical density of mixtures of plasma and substrate were measured as before, but in this experiment clearing activity has been expressed as the rate of fall in optical density in arbitrary units (ratio of optical density to time).

As well as a comparison in the two groups of the amount of clearing activity produced in response to an injection of heparin, the duration of that response was also measured. This was done by testing samples of plasma for clearing activity 48 hours after a subcutaneous injection of 250 mg. of heparin. This was carried out in both groups after six months' treatment or observation respectively.

## RESULTS

### *Inhibitor Activity of Platelet-Rich Plasma and Platelet Extracts in Ischæmic Heart Disease*

The falls in optical density of mixtures of platelet-rich plasma, standard post-heparin plasma and substrate for the 22 subjects in the two groups are shown in Table I (A). The mean values for each group, and the differences between findings in paired subjects are also shown. The mean fall in optical density was greater in the control groups (0·180) than in the ischæmic group (0·093), and the difference as analysed by a paired *t* test was statistically significant ($P = <0·01$).

The falls in optical density of mixtures of platelet extracts, standard post-heparin plasma and substrate for the two groups are shown in Table I (B). The mean fall in optical density was again greater in the control group (0·338) than in the ischæmic group (0·265), and the difference was statistically significant ($P = <0·05$).

TABLE I

*Falls in Optical Density at the End of 60 Minutes of Standard Post-Heparin Plasma and Substrate with Either Platelet-Rich Plasmas (A) or Platelet Extracts (B), in Control Subjects and in Patients with Ischæmic Heart Disease*[1]

| Subject Number | A: Platelet-Rich Plasma: Fall in Optical Density at 60 Minutes (×100) | | | B: Platelet Extract: Fall in Optical Density at 60 Minutes (×100) | | | C: Platelet-Poor Plasma: Differences of Falls in Optical Density: Platelet Extract–Platelet-Rich Plasma (×100) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Controls | Infarcts | Difference | Controls | Infarcts | Difference | Controls | Infarcts | Difference |
| 1 | 0·17 | 0·14 | 0·03 | 0·20 | 0·20 | 0 | 0·03 | 0·06 | −0·03 |
| 2 | 0·29 | 0·16 | 0·13 | 0·39 | 0·29 | 0·10 | 0·10 | 0·13 | −0·03 |
| 3 | 0·06 | 0 | 0·06 | 0·15 | 0·10 | 0·05 | 0·09 | 0·10 | −0·01 |
| 4 | 0·24 | 0·03 | 0·21 | 0·38 | 0·08 | 0·30 | 0·14 | 0·05 | +0·09 |
| 5 | 0·10 | 0·05 | 0·05 | 0·14 | 0·20 | −0·06 | 0·04 | 0·15 | −0·11 |
| 6 | 0·28 | 0·21 | 0·07 | 0·34 | 0·36 | −0·02 | 0·06 | 0·15 | −0·09 |
| 7 | 0·25 | 0·08 | 0·17 | 0·13 | 0·06 | 0·07 | −0·12 | −0·02 | −0·10 |
| 8 | 0·12 | 0·11 | 0·01 | 0·26 | 0·16 | 0·10 | 0·14 | 0·05 | +0·09 |
| 9 | 0·13 | 0·09 | 0·04 | 0·66 | 0·62 | 0·04 | 0·53 | 0·53 | 0 |
| 10 | 0·21 | 0 | 0·21 | 0·29 | 0·13 | 0·16 | 0·08 | 0·13 | −0·05 |
| 11 | 0·13 | 0·15 | −0·02 | 0·78 | 0·68 | 0·10 | 0·65 | 0·53 | +0·12 |
| Mean .. | 0·18 | 0·09 | 0·09 | 0·33 | 0·26 | 0·07 | 0·16 | 0·17 | −0·11 |
| Paired *t* test | | $P = <0·01$ | | | $P = <0·05$ | | | $P$: not significant | |

[1] The calculated differences between (A) and (B) are shown in (C), and represent the probable inhibitor activities of platelet-poor plasmas.

These results showed that there was significantly more inhibitor activity in both the platelet-rich plasma and the platelet extracts of the ischæmic patients. In each instance the degree of clearing was greater in mixtures containing platelet extracts than in those containing platelet-rich plasma. There was therefore more inhibitor activity in platelet-rich plasma than in platelet extracts, the difference representing the inhibitor activity of platelet-poor plasma. These calculated differences are presented in Table I (C), which shows that the inhibitor activities of platelet-poor plasma were virtually the same in the two groups.

### *Effect on Clearing Activity of Long-Term Heparin Therapy*

Figure I shows the mean rates of clearing (fall in optical density/time expressed in arbitrary units) which were measured at intervals of several months in 10 patients who were being treated with heparin and in 10 untreated patients. In both groups the mean rates of clearing increased with time. The increase was greater in the treated than in the untreated group at the end of five months, but from the fifth to the eighth month there was a similar increase in the two groups.

Table II shows the rates of clearing in individual subjects, the mean rates of clearing and the statistical analysis of the increases in the mean rates of clearing. Seventeen of the 20 subjects showed an increase in the rate of clearing during the period of observation. The mean rates of clearing for the treated group were 0·56, 1·39 and 1·72 before treatment, and at 5·6 and 8·5 months respectively. The difference between the mean rates of clearing at 0 and at 5·6 months was highly significant ($P=<0·01$) as was the difference between 0 and 8·5 months ($P=<0·001$), but that between 5·6 and 8·5 months was not statistically significant.

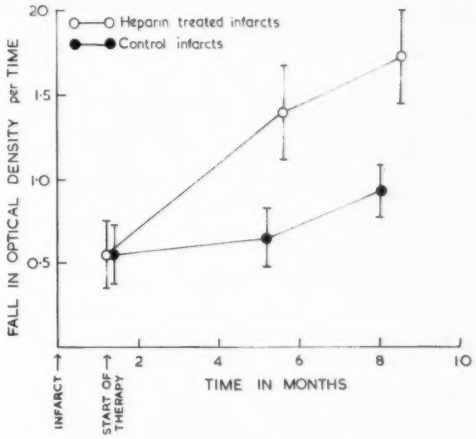


FIGURE I

The mean rates of heparin-induced plasma-clearing activities (fall in optical density per time) of a group of patients after a myocardial infarction who were being treated with intermittent injections of heparin, and a group of untreated patients (expressed in arbitrary units plus or minus the standard error)

The mean rates of clearing for the untreated group were 0·55, 0·67 and 0·94 at 0, 5·2 and 8·0 months of observation. None of the differences was statistically significant, probably because of the small number studied. The increase in the mean rates of clearing throughout the periods of observation was 1·28 for the

TABLE II

*Progressive Rates of Clearing Activities of 10 Heparin-Treated Infarct Patients and 10 Untreated Patients (Expressed in Arbitrary Units), with Analysis of the Significance of the Differences*

| Untreated Infarcts | | | | | Heparin-Treated Infarcts | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Subject | 0 | 5·2 Months | 8·0 Months | Difference between 0 and 8·0 Months | Subject | 0 | 5·6 Months | 8·5 Months | Difference between 0 and 8·5 Months |
| L.A.N. .. | 0·4 | 0·3 | 0·9 | 0·5 | R.O.D. .. | 0·2 | 0·7 | 2·2 | 2·0 |
| R.I.C. .. | 0·3 | 0·3 | 0·8 | 0·5 | A.I.R. .. | 0·4 | 2·0 | 1·2 | 0·8 |
| D.A.L. .. | 0·2 | 0·3 | 0·9 | 0·7 | C.A.M. .. | 0·2 | 0·2 | 1·2 | 1·0 |
| B.A.K. .. | 0·2 | 0·5 | 0·5 | 0·3 | F.R.Y. .. | 0·7 | 2·8 | 1·8 | 1·1 |
| T.A.R. .. | 0·8 | 0·7 | 0·9 | 0·1 | S.Y.M. .. | 0·5 | 1·1 | 2·5 | 2·0 |
| J.A.C. .. | 0·2 | 0·2 | 0·2 | 0 | D.E.N. .. | 0·3 | 0·6 | 0·3 | 0 |
| B.E.A. .. | 1·9 | 1·2 | 1·5 | −0·4 | S.M.I. .. | 2·2 | 1·5 | 1·5 | 0·5 |
| L.E.A. .. | 0·6 | 1·3 | 1·4 | 0·8 | M.I.L. .. | 0·2 | 0·5 | 0·6 | 0·4 |
| D.A.V. .. | 0·2 | 0·2 | 0·5 | 0·3 | D.I.M. .. | 0·6 | 2·5 | 2·9 | 2·3 |
| R.E.A. .. | 0·7 | 1·7 | 1·8 | 1·1 | L.O.W. .. | 0·3 | 2·0 | 3·0 | 2·7 |
| Mean±S.E. .. | 0·55±0·17 | 0·67±0·17 | 0·94±0·15 | 0·39 | Mean±S.E. .. | 0·56±0·19 | 1·39±0·28 | 1·72±0·29 | 1·28 |
| | *P* values: 0 −5·2 months: | | <0·5 | | | *P* values: 0 −5·6 months: | | <0·01 | |
| | 5·2–8·0 „ | | <0·3 | | | 5·6–8·5 „ | | >0·4 | |
| | 0 −8·0 „ | | <0·1 | | | 0 −8·5 „ | | <0·001 | |

treated group and 0·39 for the untreated group. This difference was statistically significant ($P = <0·02$).

The mean rates of clearing 48 hours after an injection of heparin were virtually identical in both groups, showing that there was no difference in the duration of clearing activity.

## DISCUSSION

These results (Table I) confirm the previous findings of Nestel and Mashford (1960) that blood platelets of patients with ischæmic heart disease contain a significantly greater amount of a substance which inhibits the heparin-induced clearing system than do the platelets of healthy subjects. These experiments also show that the difference between the two groups is confined to the inhibitor associated with platelets. The inhibitor found in platelet-poor plasma appears to be present in similar amounts in the two groups. This is in agreement with the results of Day and Wilkinson (1958), who found no difference in the inhibitory activities of platelet-poor plasma of patients with ischæmic heart disease and of age-matched control subjects.

The role of these inhibitors in the heparin-induced clearing system has been partly elucidated. After an injection of heparin, an enzyme system appears in the blood which clears turbid emulsions of fat by altering the physical state of fat particles or by hydrolysing triglycerides to fatty acids. Although the physical changes as measured by the fall in optical density are significantly correlated with the chemical changes as measured by the production of glycerol (Hollett and Nestel, 1960), exceptions have been described in which the production of unesterified fatty acids proceeded independently of changes in optical density (Havel and Peterson, 1958). These changes are influenced independently by inhibitors as shown by Hollett and Nestel (1960), who have found at least two separate inhibitors to clearing activity in human blood, one in platelets and the other in platelet-poor plasma. The platelet inhibitor was found to inhibit changes in optical density, but not lipolysis, whereas the plasma inhibitor was found to inhibit lipolysis, but not changes in optical density.

It is possible, therefore, that the increased inhibitory effect of platelets in the ischæmic group is confined to inhibition of optical clearing. The physiological role of clearing factor has not been entirely established, and the relative biological importance of physical and chemical clearing is quite unknown. The significance of the present findings is therefore uncertain.

The findings in the second experiment, in which the plasma-clearing activities of untreated and heparin-treated patients were measured at set intervals over a period of eight months, raise two points. First, the results in the untreated group are particularly interesting, because they show that soon after a myocardial infarction there is a considerable depression of heparin-induced clearing activity. During the period of observation there was a steady rise in clearing activity in the plasma of the untreated group (Figure I, Table II), although this did not reach a significant level probably because of the small numbers studied. However, it does emphasize that in studies of this nature abnormalities are likely to be greatest soon after an infarction, as Dodds and Mills (1959) have previously shown. A second point of interest is the increase in heparin-induced clearing activity over the first five months shown by the heparin-treated group. This increase was statistically significant, and was significantly greater than the rise shown by the untreated group. It confirmed similar results found previously (Nestel and Mashford, 1960). Its biological significance is uncertain, but it may be relevant to the finding of Engelberg *et alii* (1956) that patients with ischæmic heart disease treated with heparin for two years had a significantly lower mortality than untreated patients.

## ACKNOWLEDGEMENT

I wish to thank Professor R. R. H. Lovell for his helpful advice.

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# SOME OBSERVATIONS ON EJECTION SOUNDS[1]

G. R. WAGNER[2]
*From the Cardio-Vascular Diagnostic Service, Alfred Hospital, Melbourne*

SUMMARY

The properties of ejection sounds are described as they were found in a limited number of proven cases of simple pulmonary stenosis, pulmonary hypertension, congenital aortic stenosis and coarctation of the aorta.

Pulmonary ejection sounds are commonly found in pulmonary stenosis, even in severe cases. They tend to occur earlier in systole in cases of severe stenosis than in cases of mild or moderate stenosis. They vary in intensity with respiration.

In pulmonary hypertension, ejection sounds are also frequently present. They occur later in systole than in pulmonary stenosis and show little variation in intensity with respiration.

Aortic ejection sounds are commonly found in congenital aortic stenosis and in coarctation of the aorta. They occur later in systole in coarctation than in aortic stenosis, and in the former they are often less sharp and less click-like to the ear and rather broad and " split-up " phonocardiographically.

Ejection sounds are an additional physical sign in the conditions described, and they may at times be helpful in diagnosis.

ALTHOUGH references to ejection sounds can be found in the literature in the nineteenth and early in the twentieth century, particularly in French writings, it is only in recent years that they have been investigated systematically and their frequency and significance have been recognized (Minhas and Gasul, 1959). This is due to the fact that they are closely associated with the first heart sound and therefore not easy to recognize. They are high-pitched, early systolic sounds, often peculiarly clicking in quality. They are related to dilatation of the pulmonary artery or the aorta (Leatham, 1958). Pulmonary ejection sounds are therefore found in cases of pulmonary hypertension from any cause, in pulmonary valvular stenosis, and in idiopathic dilatation of the pulmonary artery. Aortic ejection sounds, on the other hand, are found in cases of aortic stenosis and regurgitation, coarctation of the aorta, Fallot's tetralogy and systemic hypertension. Generally speaking, they are more readily recognized and their incidence is more common in congenital than in acquired cardio-vascular abnormalities.

It has been a custom in this unit to perform phonocardiographic examinations on the majority of patients examined and on all those who are subjected to special investigation. This study is the outcome of the review of a limited number of proven cases of certain conditions, and it does not purport to be comprehensive in any respect. It is intended to draw attention to some points about ejection sounds which have been found interesting and useful.

## MATERIAL AND METHODS

The cases reviewed in this paper were all investigated by this unit during the past two years. Only those were selected in which special investigation, followed by operation in many instances, established the diagnosis beyond all reasonable doubt. Only those groups were selected in which ejection sounds were a striking finding.

The patients were examined clinically in a quiet room, many of them on more than one occasion. As was mentioned by Gardiner (1959), the phonocardiograph rarely records sounds which are inaudible to the stethoscope, but it greatly enhances the accurate interpretation of the auscultatory findings. This statement is supported by the present study, in that all moderate and loud ejection sounds, and the majority of the soft ones, were heard with the stethoscope even if their nature was not immediately apparent.

Phonocardiography was performed as described by Gardiner (1959), with an N.E.P. multichannel recorder.

Throughout this paper the following abbreviations will be used : ES, ejection sound ; $S_1$, first heart sound (in the time intervals indicated

[1] Received on August 29, 1960.
[2] Acting Officer-in-Charge ; at present Registrar, National Heart Hospital, London.

below, this means the first major component of the first heart sound as recorded at the apex); $S_2$, second heart sound; $Q$-$S_1$, time interval between the onset of the $QRS$ complex of the electrocardiogram and the first heart sound; $S_1$-ES, time interval between the first heart sound and the ejection sound; $Q$-ES, time interval between the onset of the $QRS$ complex of the electrocardiogram and the ejection sound.

## RESULTS

### *Simple Pulmonary Stenosis*

There were 22 patients in this group. They were all subjected to cardiac catheterization. The systolic gradient across the pulmonary valve varied from 34 to 180 mm. Hg (average 83·5 mm. Hg), except in one case, in which it was only 20 mm. Hg. The catheter could not be passed into the pulmonary artery in two cases, in both of which the presence of severe pulmonary valve stenosis was subsequently proved by operation. In all, 14 of the 22 patients were operated on, 13 by an open operation with the use of "Fluothane" and heparin (Orton and Morris, 1959), and one by an operation in which a pump-oxygenator was used. The last-mentioned patient had shown evidence of infundibular stenosis at cardiac catheterization, and was seen at operation to have extreme valvular stenosis and marked hypertrophy of the right ventricular outflow tract. Two patients had evidence of an associated lesion. Both had atrial septal defects with right-to-left shunts; one was operated upon. This last-mentioned patient, and the patient operated upon with the aid of the pump oxygenator, were the two who died in this series.

Of the 22 cases, ejection sounds were present unequivocally in 16. In two no ejection sound was present, in four it was doubtfully present, in one it was soft, in six it was moderate, and in nine it was loud. These sounds were most obtrusive to the ear in cases of mild or moderate stenosis, but they were also present in three of the four cases in which there were systolic gradients greater than 140 mm. Hg across the pulmonary valve. The most severe case in this group merits particular attention.

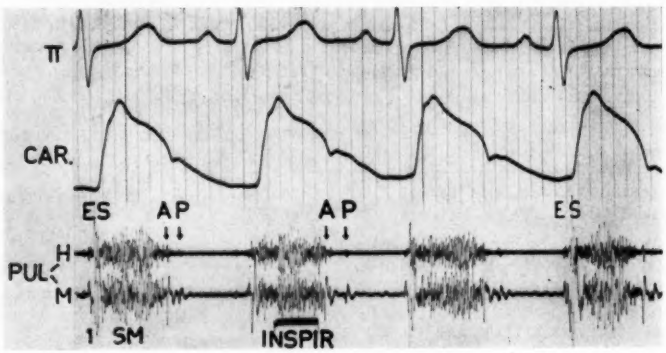



FIGURE I

Simple pulmonary stenosis in a girl, aged three years. Simultaneous high frequency (H) and medium frequency (M) records in the pulmonary area (PUL), showing a loud ejection sound (ES) 0·02 second after the first heart sound (1), and at the beginning of a loud, diamond-shaped systolic murmur (SM), which runs up to the aortic element (A) of the second heart sound. The latter is followed after 0·04 second by a soft pulmonary element (P), the interval between the two elements increasing on inspiration to 0·06 second. The ejection sound decreases markedly in intensity on inspiration (INSPIR). The $Q$-ES interval is 0·08 second. Reference tracings in this and in the succeeding figures are the electrocardiogram (II) with or without the carotid pulse tracing (CAR). Time markings here and in subsequent tracings every 0·04 second

This patient was a girl, aged 22 years, mentioned earlier as having been operated upon with the aid of the pump oxygenator. In her case a sound was recorded in the pulmonary area which was short and sharp and decreased in intensity on inspiration. It occurred 0·06 second after the onset of the $QRS$ complex of the electrocardiogram, and almost certainly represents an ejection sound. However, as no first heart sound was recorded, this is not proved beyond doubt.

The ejection sounds tended to occur earlier in systole in the severe cases than in the mild cases. Of the 16 patients who had definite ejection sounds, 11 had systolic pressure gradients less than, and 5 had systolic pressure gradients greater than, 100 mm. Hg across the pulmonary valve. In the first group the average duration of $Q$-ES was 0·089 second (range 0·08 to 0·11 second, with one case of 0·06 second); in the second group it was 0·068 second (range 0·06 to 0·08 second). The time intervals $Q$-$S_1$, $S_1$-ES, and $Q$-ES, for the whole group, showed average values of 0·05 second (range 0·03 to 0·07 second), 0·033 second (range 0·02 to 0·05 second) and 0·08 second (range 0·06 to 0·11 second) respectively. Figure I shows the findings in a case of moderate severity. The patient was a girl, aged three years, who at cardiac catheterization had a right ventricular systolic pressure of 64 mm. Hg and a systolic gradient across the pulmonary valve of 55 mm. Hg. A well-marked ejection sound is shown 0·02 second after the first heart sound. The $Q$-ES interval is 0·08 second.

It is of interest that over the period during which these 22 cases of simple pulmonary stenosis were seen, there were six cases of isolated infundibular pulmonary stenosis, in all of which cardiac catheterization was performed. In none was there any evidence of a shunt. In two cases the diagnosis was confirmed at open operation, and in one the absence of a right-to-left shunt was confirmed by angiocardiography. In none of these cases was an ejection sound heard or recorded.

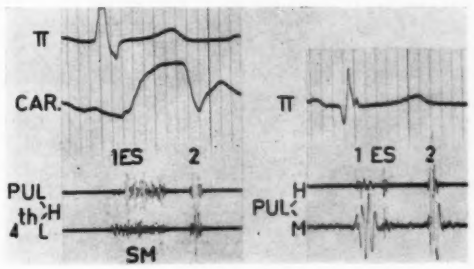
### *Pulmonary Hypertension*

This group was arbitrarily limited to cases in which the pulmonary artery systolic pressure at cardiac catheterization was 80 mm. Hg or higher. The underlying anatomical abnormality was disregarded. There were 21 cases, 3 of rheumatic mitral valve disease and 18 of congenital cardiac anomalies. Of these 21 cases, in 2 there were no ejection sounds, in 4 the presence of an ejection sound was in doubt, in 7 there were soft ejection sounds, and in 8 there were moderate ejection sounds. In the 15 patients with definite ejection sounds the mean $Q$-$S_1$ interval was 0·07 second (range 0·05 to 0·10 second), the mean $S_1$-ES interval was 0·05 second (range 0·03 to 0·08 second), and the mean $Q$-ES interval was 0·12 second (range 0·10 to 0·18 second). Figure II shows the findings in two of these cases. Tne $Q$-ES intervals in (*a*) and (*b*) are 0·11 and 0·16 second respectively.

In many cases of pulmonary hypertension cardiac catheterization is not indicated. This applies to most of those patients showing definite central cyanosis on clinical examination. Ejection sounds are present in many of these, and are not fundamentally different from the ones found in the group analysed.

### *Congenital Aortic Stenosis*

There were five patients in this group, all of whom were operated upon. Three had valvular stenosis, one had subvalvular stenosis and one had supravalvular stenosis. In two of the cases of valvular stenosis and in the case of supravalvular stenosis, ejection sounds were present. The mean values for the $Q$-$S_1$, $S_1$-ES and $Q$-ES intervals were approximately 0·05, 0·05 and 0·10 second respectively. Figure III shows the findings in one of these cases. The ejection sound was widely recorded, but was maximal at the apex. The $Q$-ES interval is 0·11 second.




(*a*) (*b*)

FIGURE II

Records in two cases of proven pulmonary hypertension. In (*a*), high-frequency (H) tracings in the pulmonary area (PUL) and fourth left intercostal space (4th L) show a soft first heart sound (1), a moderate ejection sound (ES) and an early systolic murmur (SM), and a loud second heart sound (2). The $Q$-ES interval is 0·11 second. At cardiac catheterization the pulmonary artery pressure was 90/48 mm. Hg. In (*b*), at the pulmonary area (PUL), there are a low-pitched first heart sound (1), an ejection sound (ES) and a loud second heart sound (2). The $Q$-ES interval is 0·16 second. The pulmonary artery pressure at cardiac catheterization was 104/60 mm. Hg

### *Coarctation of the Aorta*

This group comprises 11 patients, all of whom were operated upon. Two of these had considerable aortic incompetence, the others had none, or only minor aortic valve lesions. In every case an ejection sound was recorded. It was soft in 3 cases, moderate in 5 and loud in 3. The mean values of the $Q$-$S_1$, $S_1$-ES and $Q$-ES intervals were 0·06, 0·07 and 0·13 second respectively. In several cases the ejection sounds were rather broad and "split-up" on the phonocardiogram. This quality could

be appreciated on auscultation, in that the sound was less click-like and more like a normal first heart sound. Figure IV shows the findings in two of these cases. In (*a*) the ejection sound is " split-up ".

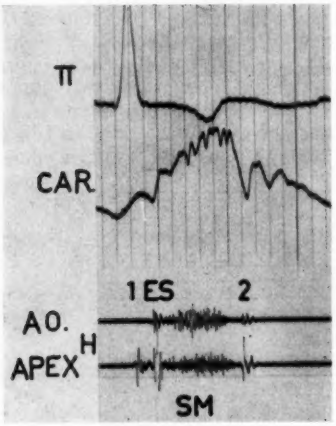



FIGURE III

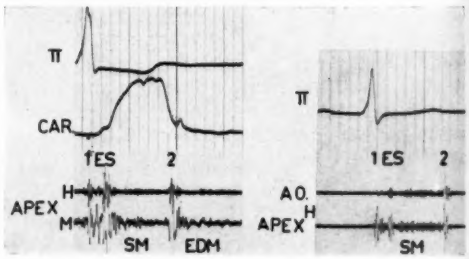
Congenital valvular aortic stenosis in a boy, aged 12 years. Simultaneous high-frequency (H) records in the aortic area (AO) and at the apex, showing the first heart sound (1), a clear ejection sound (ES) which is louder at the apex than in the aortic area, a diamond-shaped systolic murmur (SM) and a second heart sound (2). The *Q*-ES interval is 0·11 second. The carotid pulse tracing (CAR) is slow-rising and shows coarse serrations

## DISCUSSION

The properties of ejection sounds as they occur in several well-defined conditions have been described. These sounds, which are also called early systolic clicks or ejection clicks, occur in close association with the first heart sound. Indeed, it can be difficult to distinguish them from a widely split first heart sound as it occurs in complete right bundle branch block, or even from a normal first heart sound when this is preceded by a fourth heart sound. However, they are generally different in character from the first heart sound, being short, sharp, or even clicking and high-pitched.

As this report deals with selected material, the incidence of ejection sounds in the conditions cited does not have general validity. It is also not intended to discuss the mode of production of these sounds. This subject is dealt with in detail by Minhas and Gasul (1959), who come to the conclusion that ejection sounds in valvular stenosis originate at the valve, whereas in other cases with such sounds an origin in the wall of the dilated vessel is more likely. This conclusion is in contrast to the findings of Leatham and Vogelpoel (1954), Leatham and Weitzman (1957) and Crevasse and Logue (1958), who suggested an origin of ejection sounds in the wall of the dilated pulmonary artery in pulmonary stenosis as well as in pulmonary hypertension.

As was mentioned earlier, ejection sounds are related to dilatation of the pulmonary artery or the aorta (Leatham, 1958). Pulmonary ejection sounds can be subdivided into two groups, those which are associated with normal or low pulmonary artery pressures and those which are associated with raised pulmonary artery pressures. The former vary in intensity from patient to patient, and when loud, they may be audible all over the precordium; but they usually have a site of maximum intensity in the pulmonary area or in the third or first left intercostal spaces. They may be palpable. They show considerable and often striking variation in intensity with respiration, becoming softer on inspiration (Figure I). This feature may be so pronounced that they can disappear from one heart beat to the next. This finding, once appreciated, can hardly be misinterpreted.




(*a*) (*b*)

FIGURE IV

Tracings taken from two patients with coarctation of the aorta; (*a*) simultaneous high-frequency (H) and medium-frequency (M) records at the apex, and (*b*) simultaneous high-frequency (H) records at the aortic area (AO) and at the apex, showing a first heart sound (1), an ejection sound (ES), a systolic murmur (SM), a second heart sound (2), and in (*a*) an early diastolic murmur (EDM). In (*a*) the ejection sound is broad, a feature commonly seen in coarctation of the aorta

In severe pulmonary valvular stenosis, the ejection sound may occur so early as to simulate the first heart sound; but its nature is usually revealed by its character and its variation with respiration, and by the fact that it is uncommon to hear or record a loud first sound at the base. It has been maintained by Leatham and Weitzman (1957) and by Crevasse and Logue

(1958) that ejection sounds are uncommon in severe simple pulmonary stenosis. In contrast thereto, this study suggests that ejection sounds, while frequently less striking and less easy to recognize than in mild or moderate pulmonary stenosis, are nevertheless often present in severe cases. In this connexion, the following observation by Leatham and Vogelpoel (1954) is of interest :

> . . . we have not heard an extra pulmonary sound in any patient with severe pulmonary stenosis and dilatation of the pulmonary artery and have only once recorded it. We have often noticed in these cases a loud clicking first heart sound at the base which might be ascribed to superimposition of a pulmonary sound on major components of the first sound.

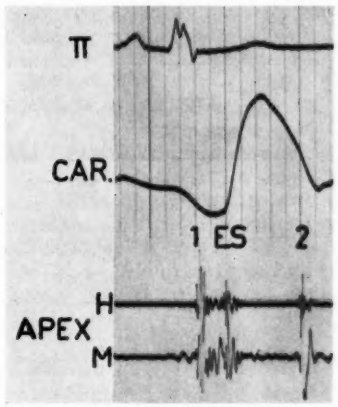



FIGURE V

A severe case of Fallot's tetralogy. Simultaneous high-frequency (H) and medium-frequency (M) records at the apex, showing the first heart sound (1), an ejection sound (ES), and the second heart sound (2)

As many writers have shown in the past, ejection sounds are frequently present in patients with pulmonary hypertension. Under these circumstances, they show less variation in intensity with respiration and occur somewhat later in systole than in patients with low or normal pulmonary artery pressures. These findings are confirmed, and the actual time relationships of these sounds, as found in this study, show close agreement with those found by Minhas and Gasul (1959).

In a small number of cases of isolated infundibular pulmonary stenosis no ejection sounds were recorded.

Aortic ejection sounds are usually maximal at the apex, less commonly at the lower left sternal edge or the aortic area. They are heard more widely over the precordium than pulmonary ejection sounds, and show little or no variation in intensity with respiration. Their character varies considerably. They may be clicking or they may be less high-pitched and less sharp, approaching the quality of a first heart sound; the latter variety is found particularly in coarctation of the aorta. They occur later in systole in coarctation of the aorta than in aortic stenosis, the mean *Q*-ES interval in these two conditions being 0·13 and 0·10 second respectively. Minhas and Gasul (1959) found the *Q*-ES intervals in a group of cases of congenital aortic stenosis and in a group of cases in which aortic ejection sounds were present without aortic stenosis to be 0·11 and 0·12 second respectively. Thus the present finding of a prolonged *Q*-ES interval in coarctation of the aorta lends support to the concept elaborated by these writers, that the degree of delay of an ejection sound is related to the duration of isometric contraction of the ventricle in question, in this instance the left one, and this would be expected to be prolonged in coarctation on account of the raised pressure in the ascending aorta.

Aortic ejection sounds may also be present in Fallot's tetralogy, usually in severe cases. The findings in such a case are illustrated in Figure V.

ACKNOWLEDGEMENTS

I wish to thank Dr. James M. Gardiner for most valuable help in the preparation of this paper. I am grateful to Mr. K. N. Morris and Mr. C. J. Officer Brown, Honorary Thoracic Surgeons, and to other members of the Thoracic Surgical Unit of the Alfred Hospital, for permission to study their patients, and to Miss H. M. Anderson, Miss J. L. Taylor and Miss J. M. Wright for their technical help.

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# PULMONARY DIFFUSING CAPACITY IN CHRONIC OBSTRUCTIVE LUNG DISEASE: STUDIES AT REST AND ON EXERCISE BY THE STEADY STATE, PHYSIOLOGICAL DEAD SPACE METHOD[1,2]

ROBERT A. B. HOLLAND[3] AND RALPH B. BLACKET[4]
*From the Department of Medicine, University of Sydney*

SUMMARY

Studies of 19 cases of chronic obstructive lung disease are reported. The mean value for the ratio of residual volume to total lung capacity in the series was 0·61, and the mean maximum breathing capacity was 31 L/min.

Arterial blood gas findings were confirmatory of those of other workers, arterial oxygen unsaturation at rest, frequently relieved on exercise, being common. Minor degrees of carbon dioxide retention were common.

An increase in physiological dead space and in the ratio of dead space to tidal volume was found in nearly all cases at rest and in most cases on exercise.

Diffusing capacity for carbon monoxide ($D_{CO}$) was estimated by the steady state " Filley " method. Resting $D_{CO}$ was reduced in all cases, the reduction being extreme in some. The mean was 7·2 ml./min./mm. Hg. In all patients able to exercise, diffusing capacity rose, but the values on exercise were well below those of normal subjects exercising at the same level of oxygen consumption. $D_{CO}$ reduction did not correlate with arterial oxygen unsaturation or with the degree of airway obstruction.

Some of the lowering of $D_{CO}$ is attributed to the presence of non-uniformity in the lungs, but a true reduction does appear to be present. Possible explanations are discussed of the frequent finding by others that single-breath $D_{CO}$ is little reduced in this condition.

THE organization of the lung is directed to the rapid exchange of inspired oxygen entering the alveoli with carbon dioxide in the pulmonary capillary blood. The capacity of the lung to absorb oxygen from the alveoli into the red cells passing through the surrounding capillaries is obviously of critical importance at high altitudes, in exercise and in pulmonary disease. The pulmonary diffusing capacity, which is expressed in millilitres of gas per millimetre of mercury pressure gradient between the alveoli and the pulmonary capillary blood, provides a measure of this aspect of pulmonary function. Because it resembles oxygen in molecular size, diffusibility and affinity for hæmoglobin, carbon monoxide in low or " tracer " concentrations lends itself readily to the estimation of pulmonary diffusing capacity.

In emphysema[1] there is a breaking-down of alveolar septa with a concomitant loss of pulmonary capillaries. The alveolo-capillary surface area is lessened, and for this reason a decrease in the pulmonary diffusing capacity is to be expected, although the thickness of the alveolo-capillary membrane is not increased. Measurements of diffusing capacity in this condition have given conflicting results. Measured by the two-level oxygen method, the diffusing capacity has been found lowered at rest in the more severe cases (Donald *et alii*, 1952) and lowered on exercise in most cases (Shepard *et alii*, 1955). The steady-state carbon monoxide method of Bates, Boucott and Dormer (1955) has also been used; low values for carbon-monoxide diffusing capacity ($D_{CO}$) were found at rest; on exercise one group found little if any rise in $D_{CO}$ (Bates *et alii*, 1956) while

[1] Received on May 27, 1960.
[2] This investigation was supported in part by the National Health and Medical Research Council and the Joint Coal Board.
[3] Present address: Department of Physiology, Graduate School of Medicine, University of Pennsylvania.
[4] Present address: Department of Medicine, University of New South Wales.

[1] The Ciba Foundation Symposium on terminology in emphysema and related conditions (Ciba Report, 1959) has recommended the use of the term " chronic obstructive lung disease " rather than " emphysema " unless anatomical evidence of emphysema is available. This recommendation reflects the uncertainty of the clinical diagnosis of emphysema and has been adopted here when the disease in the clinical sense is intended.

another group found that there was often a considerable rise (MacNamara *et alii*, 1959). The most commonly used method of estimating diffusing capacity has been a modification of the single-breath carbon monoxide method first described by M. Krogh in 1915. The single-breath $D_{CO}$ has been found within or close to normal limits in many cases and severely reduced in only a few. A rebreathing method has given results for $D_{CO}$ often within the normal range (Kjerulf-Jensen and Kruhøffer, 1954; Lewis *et alii*, 1959). The method of Filley *et alii* (1954), which makes use of physiological dead space in determining $D_{CO}$, has been used in some cases, and the usual finding has been a considerable lowering of $D_{CO}$ (Lewis *et alii*, 1959; Williams and Zohman, 1959). A modification of the Filley method has given results little different from normal, and agreeing well with those found by the single-breath method (Marshall, 1958).

In the following paper are presented the results of a study of diffusing capacity by the method of Filley *et alii* in 19 cases of emphysema and obstructive lung disease, the estimations having been made at rest and, when possible, on exercise also. As the Filley method requires ventilation, arterial blood gas and dead space estimations, these findings are included as an integral part of the report.

## METHODS

The methods used for testing pulmonary function have been described in detail elsewhere (Holland and Blacket, 1958, 1959). Lung volumes were measured on a six-litre Knipping spirometer, the functional residual capacity (FRC) being determined by the closed-circuit helium-dilution method. Maximum breathing capacity (M.B.C.) was determined over 12 seconds' breathing on the closed circuit. Diffusing capacity for carbon monoxide was determined by the method of Filley *et alii* (1954), carbon monoxide in air being measured with an infra-red analyser. Arterial carbon dioxide tension was read from a nomogram (Singer and Hastings, 1948), with a knowledge of arterial blood pH, carbon dioxide content and hæmatocrit. Dead space was measured by the Bohr equation, arterial carbon dioxide tension being taken as alveolar tension. The inspired carbon monoxide concentration was about 0·05%. In one case (G.S.), carbon monoxide was determined by the iodine pentoxide method (Adams and Simmons, 1951), the inspired concentration being 0·14%. The carbon monoxide mixture was breathed for three minutes at rest and for two minutes on exercise, to allow a steady state of carbon monoxide breathing to be achieved before collection of blood or expired gas was commenced. A period of five minutes was allowed on exercise before carbon monoxide breathing began.

## THE SUBJECTS STUDIED

The first 16 patients had been diagnosed as suffering from chronic generalized emphysema by the referring physicians and by us on clinical grounds, supported by radiological evidence in several cases. The last three patients (J.G., L.M. and C.T.) also had a history of pulmonary tuberculosis, and their condition was due in part at least to post-tuberculosis scarring. For selection, all patients were required to have a ratio of residual volume to total lung capacity (R.V./T.L.C.) greater than 45%, and greater than the value predicted for a normal subject by the formulæ of Needham *et alii* (1954). A maximum breathing capacity of less than 60% of that predicted was also required. Some of the patients did not show an increase in T.L.C., but were not excluded if the other criteria were fulfilled. The presence of bullæ was not a ground for exclusion, but patients with significant dust exposure were not included. S.W. had a small coincidental peripheral coin shadow, apparently localized.

Of the 19 patients studied, 17 were males and two were females. Their ages ranged from 43 to 76 years, and the mean age was 59 years. Fuller information is given in Table I. Almost all the patients had a history of cough, sputum and increasing breathlessness of some years' duration. The severity of the cough and the amount of the sputum varied, and in four subjects (C.B., G.C.S., J.G. and C.T.) these symptoms were not prominent. Only two patients (A.F. and A.S.) had a definite history of right-sided cardiac failure at the time of testing. An accurate history in terms of duration of symptoms is difficult to obtain in emphysema; first, most patients have been smokers and have not taken notice of their "cigarette cough"; and secondly, the onset of the disability is usually gradual and the patient limits his activity, not feeling breathless until the disease is far advanced or a chest infection causes sudden worsening of his condition.

## RESULTS

### *Lung Volumes, Maximum Breathing Capacity and Intrapulmonary Gas Mixing*

Detailed results for lung volumes and M.B.C. are shown in Table I. The mean value for the ratio R.V./T.L.C. was 61%, and the mean M.B.C. was 31 litres per minute. In addition,

TABLE I

*Physical Data, Lung Volumes and Maximum Breathing Capacity of the Subjects*

| Patient | Age (Years) and Sex | Body Surface Area (sq. m.) | Total Lung Capacity (TLC) | | Vital Capacity | | Functional Residual Capacity | | Residual Volume (RV) | | RV/TLC | | Maximum Breathing Capacity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Litres | Percentage Predicted[1] | Litres | Percentage Predicted[1] | Litres | Percentage Predicted[1] | Litres | Percentage Predicted[1] | Percentage | Percentage Predicted[1] | Litres per Minute | Percentage Predicted[1] |
| C.B. | 65, F. | 1·50 | 3·66 | 96 | 1·67 | 82 | 2·44 | 110 | 1·93 | 108 | 52·7 | 117 | 27 | 40 |
| A.D. | 63, M. | 1·48 | 4·92 | 83 | 2·05 | 67 | 3·62 | 91 | 2·51 | 87 | 51·0 | 106 | 48 | 57 |
| S.F. | 47, M. | 1·63 | 10·39 | 156 | 3·31 | 83 | 7·98 | 192 | 6·78 | 254 | 65·3 | 158 | 32 | 30 |
| A.F. | 60, M. | 1·58 | 5·75 | 94 | 2·48 | 75 | 4·01 | 101 | 2·92 | 104 | 50·8 | 110 | 52 | 57 |
| A.H. | 76, M. | 1·52 | 4·98 | 102 | 2·22 | 100 | 3·47 | 109 | 2·57 | 96 | 51·7 | 103 | * | |
| J.H. | 58, M. | 1·77 | 7·68 | 123 | 2·54 | 71 | 5·86 | 156 | 5·06 | 191 | 65·9 | 153 | 28 | 28 |
| C.L. | 58, M. | 1·65 | 7·47 | 111 | 2·63 | 71 | 5·48 | 124 | 4·95 | 164 | 66·3 | 142 | 23 | 24 |
| M.N. | 68, M. | 1·74 | 5·34 | 91 | 1·87 | 61 | 3·76 | 103 | 3·31 | 119 | 62·0 | 132 | 39 | 44 |
| T.P. | 43, M. | 1·49 | 5·81 | 106 | 1·88 | 54 | 4·61 | 148 | 3·77 | 187 | 64·9 | 178 | 19 | 18 |
| F.R. | 59, M. | 1·28 | 5·25 | 106 | 1·93 | 75 | 3·98 | 122 | 3·23 | 135 | 61·5 | 136 | 24 | 30 |
| I.S. | 49, F. | 1·44 | 3·73 | 93 | 1·46 | 61 | 2·58 | 106 | 2·28 | 139 | 61·1 | 150 | 18 | 23 |
| G.C.S. | 61, M. | 1·82 | 5·95 | 96 | 2·87 | 82 | 3·70 | 100 | 2·81 | 105 | 47·2 | 108 | 55 | 55 |
| A.S. | 56, M. | 1·66 | 7·14 | 117 | 2·51 | 72 | 5·75 | 153 | 4·62 | 177 | 64·7 | 150 | 21 | 21 |
| G.S. | 51, M. | 1·68 | 5·71 | 100 | 1·92 | 55 | 4·10 | 127 | 3·75 | 168 | 65·6 | 170 | 34 | 32 |
| J.T. | 62, M. | 1·40 | 5·98 | 101 | 1·44 | 48 | 5·36 | 132 | 4·16 | 144 | 69·6 | 143 | 24 | 29 |
| S.W. | 69, M. | 1·58 | 7·29 | 124 | 1·84 | 63 | 6·04 | 153 | 5·51 | 186 | 75·6 | 152 | 21 | 26 |
| J.G. | 57, M. | 1·83 | 7·47 | 118 | 2·39 | 65 | 6·03 | 162 | 5·18 | 198 | 69·3 | 167 | 19 | 18 |
| L.M. | 54, M. | 1·88 | 3·68 | 56 | 1·46 | 37 | 2·52 | 65 | 2·10 | 79 | 57·1 | 139 | 33 | 30 |
| C.T. | 63, M. | 1·71 | 5·55 | 86 | 2·57 | 74 | 4·02 | 96 | 2·96 | 99 | 53·3 | 113 | 39 | 42 |

[1] Predictions by the formulæ of Needham *et alii* (1954).
* Patient too distressed to perform M.B.C. test.

all patients had delay in the intrapulmonary mixing of helium. An exact index was not calculated, as it was thought that an index calculated from the closed-circuit dilution curves would not furnish useful information for comparison of this with other series in which diffusing capacity has been measured.

## BLOOD GASES

The blood gas findings are set out in Table II.

The arterial oxygen saturation (uncorrected for dissolved oxygen) was low at rest in many cases, but normal in others. The mean resting value was low—91·9%. The normal range in this laboratory is from 93% to 98%. Of the nine patients able to exercise, the arterial oxygen saturation rose in seven and fell in two; in this group of nine cases, the mean resting saturation was 91·6% and the mean exercise saturation was 94·2%.

Arterial carbon dioxide tension (measured after connexion to the valves) was higher than in normal subjects. The mean for this series was 42·7 mm. Hg. The mean for normal subjects in this laboratory was 37·5 mm. Hg, and the range 28·2 to 42·0 (Holland and Blacket, 1958). In three cases (A.F., G.C.S. and A.S.) the figures for blood gases before and after connexion to the mouthpiece are given to show the change which may occur. Eight of the patients had an arterial carbon dioxide tension at rest or on exercise greater than 44 mm. Hg. None of the normal subjects reported by us previously had such a high tension at rest or at the low levels of exercise reached by the patients. The high carbon dioxide tensions were associated with levels of alveolar ventilation less than the value predicted for a normal subject at that oxygen consumption by the equation found previously (Holland and Blacket, 1958).

The blood-gas findings are substantially similar to those of other workers (Baldwin *et alii*, 1949*b*; West *et alii*, 1951; Fishman *et alii*, 1955; Stuart-Harris and Hanley, 1957; Williams and Zohman, 1959). However, one difference is noted. The two patients with the highest resting values for arterial carbon dioxide tension were T.P. and J.G., with tensions of 50 and 55 mm. Hg respectively. Both patients had low alveolar ventilation. Their arterial oxygen saturations were 96·6% and 94·6% respectively; Baldwin *et alii*, in their study of 122 patients, found no patient with carbon dioxide retention whose saturation was as high as this. Williams and Zohman also found that in nearly all their patients carbon dioxide retention was less prominent than arterial oxygen unsaturation.

### *Physiological Dead Space*

The physiological dead space was raised in nearly all cases. In absolute figures, only patients C.B., T.P. and G.S. had a resting dead space within two standard deviations of the mean found for normal subjects of the

appropriate sex (Holland and Blacket, 1958). The mean dead space in the present series was 232 ml. The mean for normal subjects was 133 ml. These means are significantly different by the $t$ test ($P<0{\cdot}001$). On exercise the dead space always rose.

The ratio $V_D/V_T$, both corrected for the mouthpiece ($V_D(C)/V_T(C)$), at rest was greater than 0·30 in all cases. In many it was very high, and its mean value was 0·50. The ratio was little altered on exercise.

In normal subjects, $V_D$ and $V_D/V_T$ can be underestimated in shallow breathing; the shape of the valve box makes it likely that under these circumstances not all of it is functionally "dead", and the subtraction of an excessive figure for mouthpiece dead space can lead to distinctly low values. In emphysema, shallow breathing is the rule, and so dead space has probably been underestimated in the results shown.

### *Ventilation and Alveolar Ventilation*

The mean ventilation for the group both at rest and on exercise was significantly higher than for our normal subjects (Table II, Figure I). Alveolar ventilation was little different from normal ventilation at rest, but was lower than normal on exercise (Figure II). A raised ventilation with a normal or reduced alveolar ventilation is merely an indication of high physiological dead space, its effect being enhanced in emphysema by the tendency to shallow breathing.

### *Dyspnœa*

Dyspnœa after exercise was recorded in four cases. In C.L. and F.R., whose exercise ventilation exceeded the M.B.C., the dyspnœa was graded as severe and maximal respectively. In J.H. and G.C.S. it was graded as very mild and mild respectively, the respective breathing reserves being 45% and 55%.[1] The degree of dyspnœa for a given breathing reserve was much less than we found in cases of pulmonary fibrosis (Holland and Blacket, 1960, 1961). This is in keeping with the findings of Baldwin *et alii* (1949*a*, 1949*b*).

[1] The breathing reserve is maximum breathing capacity minus the actual ventilation at the moment expressed as a percentage of the maximum breathing capacity.

TABLE II

*Results of Ventilation, Blood-Gas, and Diffusion Studies in Emphysema*

| Patient | $O_2$ Consumption (ml./min.) | Ventilation (l./min.) | Alveolar Ventilation (l./min./sq. m.) | Arterial Blood: Packed Cell Volume | Arterial Blood: $O_2$ Saturation of Hb (Percentage) | Arterial Blood: $CO_2$ Content (mM./L.) | Arterial Blood: pH | Arterial Blood: $CO_2$ Tension (mm. Hg) | $V_D(C)$ (ml.)[1] | $\frac{V_D(C)}{V_T(C)}$[1] | Respiratory Exchange Ratio | Fractional CO Uptake (Percentage) | $\frac{F_{ACO}}{F_{ICO}}$ | $D_{CO}$ (ml./min./mm. Hg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C.B. | 179[2] | 5·97 | 2·18 | 0·37 | 92·5 | 22·3 | 7·42 | 39·9 | 99 | 0·32 | 0·84 | 35 | 0·32 | 8·1 |
| | 474 | 15·14 | 6·22 | 0·40 | 94·0 | 21·2 | 7·37 | 42·3 | 162 | 0·36 | 0·96 | 37 | 0·37 | 18·4 |
| A.D. | 194[2] | 10·30 | 2·84 | 0·25 | 97·3 | 22·5 | 7·45 | 35·1 | 222 | 0·52 | 0·89 | 18 | 0·55 | 4·0 |
| S.F. | 229[2] | 11·75 | 2·32 | 0·43 | 93·5 | 23·3 | 7·44 | 40·5 | 299 | 0·64 | 0·77 | 22 | 0·31 | 9·8 |
| A.F. | — | — | — | 0·43 | 89·9 | 25·0 | 7·44 | 44·0 | — | — | — | — | — | — |
| | 222[2] | 11·54 | 3·31 | — | — | 24·2 | 7·50 | 37·8 | 242 | 0·48 | 1·03 | 25 | 0·45 | 7·5 |
| | 552[2] | 19·67 | 6·57 | 0·47 | 94·8 | 23·6 | 7·39 | 46·2 | 342 | 0·43 | 1·00 | 23 | 0·54 | 10·3 |
| A.H. | 222[2] | 9·81 | 2·90 | 0·44 | 89·2 | 22·5 | 7·46 | 38·0 | 280 | 0·49 | 0·88 | 24 | 0·48 | 5·6 |
| J.H. | 245[2] | 8·58 | 2·57 | 0·40 | 94·3 | 24·5 | 7·42 | 43·6 | 220 | 0·41 | 0·93 | 32 | 0·36 | 8·9 |
| | 430[2] | 15·30 | 4·68 | 0·43 | 96·2 | 24·0 | 7·44 | 41·2 | 292 | 0·41 | 0·94 | 29 | 0·47 | 10·9 |
| C.L. | 201[2] | 8·52 | 2·45 | 0·40 | 93·8 | 21·3 | 7·45 | 36·1 | 245 | 0·47 | 0·82 | 31 | 0·35 | 8·8 |
| | 659[2] | 27·86 | 9·16 | 0·43 | 96·9 | 19·7 | 7·40 | 36·9 | 438 | 0·43 | 0·97 | 26 | 0·53 | 15·6 |
| M.N. | 277[2] | 10·90 | 2·90 | 0·37 | 92·7 | 24·0 | 7·40 | 43·6 | 223 | 0·47 | 0·92 | 26 | 0·45 | 7·3 |
| | 495 | 17·78 | 5·02 | 0·39 | — | 23·4 | 7·39 | 45·6 | 285 | 0·45 | 0·93 | 25 | 0·50 | 10·2 |
| | 689 | 21·17 | 6·58 | 0·39 | 88·7 | 23·8 | 7·36 | 48·0 | 328 | 0·41 | 0·92 | 25 | 0·55 | 11·0 |
| T.P. | 215[2] | 7·92 | 2·13 | 0·44 | 96·6 | 26·8 | 7·41 | 50·3 | 133 | 0·49 | 0·85 | 26 | 0·35 | 6·5 |
| F.R. | 177[2] | 7·28 | 2·54 | 0·41 | 90·5 | 26·2 | 7·46 | 43·8 | 348 | 0·51 | 0·92 | 26 | 0·42 | 5·3 |
| | 705 | 30·79 | 10·20 | 0·44 | 99·9 | 22·5 | 7·33 | 48·7 | 461 | 0·54 | 1·03 | 19 | 0·56 | 12·0 |
| I.S. | 206[2] | 8·24 | 2·39 | 0·43 | 89·1 | 23·6 | 7·40 | 44·4 | 182 | 0·50 | 0·85 | 25 | 0·41 | 5·7 |
| | 484 | 16·79 | 5·47 | 0·48 | 88·0 | 22·4 | 7·31 | 52·2 | 301 | 0·48 | 0·98 | 24 | 0·50 | 9·3 |
| G.C.S. | — | — | — | 0·41 | 94·2 | 22·4 | 7·43 | 38·8 | — | — | — | — | — | — |
| | 292[2] | 8·79 | 2·97 | 0·41 | — | 22·7 | 7·43 | 40·0 | 317 | 0·34 | 0·85 | 30 | 0·53 | 5·9 |
| | 800[2] | 25·36 | 9·00 | 0·43 | 96·9 | 20·7 | 7·40 | 39·6 | 397 | 0·30 | 0·96 | 21 | 0·49 | 12·0 |
| A.S. | — | — | — | — | 95·9 | 24·7 | 7·45 | 41·7 | — | — | — | — | — | — |
| | 204[2] | 8·34 | 2·22 | 0·42 | — | 24·7 | 7·47 | 40·0 | 189 | 0·49 | 0·82 | 27 | 0·40 | 6·6 |
| G.S. | 239[2] | 9·31 | 2·30 | 0·51 | 87·4 | 24·3 | 7·44 | 43·9 | 158 | 0·49 | 0·83 | 31 | 0·27 | 12·6 |
| | 551[2] | 17·85 | 6·37 | 0·51 | 92·7 | 19·8 | 7·41 | 37·7 | 199 | 0·28 | 0·84 | 31 | 0·48 | 13·6 |
| J.T. | 219[2] | 11·75 | 2·34 | 0·40 | 84·2 | 26·6 | 7·41 | 48·5 | 195 | 0·63 | 0·84 | 18 | 0·35 | 7·5 |
| S.W. | 214[2] | 9·92 | 2·32 | 0·35 | 90·1 | 25·5 | 7·39 | 47·5 | 301 | 0·58 | 0·93 | 22 | 0·41 | 6·3 |
| J.G. | 254 | 8·52 | 1·85 | 0·38 | 94·6 | 29·1 | 7·39 | 55·0 | 213 | 0·52 | 0·84 | 29 | 0·29 | 10·6 |
| L.M. | 285[2] | 11·33 | 2·60 | 0·41 | 88·4 | 25·7 | 7·45 | 43·9 | 306 | 0·52 | 0·86 | 21 | 0·52 | 5·3 |
| C.T. | 242[2] | 10·10 | 2·60 | 0·39 | 91·6 | 23·6 | 7·43 | 40·3 | 238 | 0·50 | 0·88 | 21 | 0·35 | 5·3 |

[1] Physiological dead space and tidal volume both corrected for dead space of mouthpiece.
[2] Mean of duplicates.

*Fractional Carbon-Monoxide Uptake*

Fractional carbon-monoxide uptake ($CO_F$) was reduced in all cases. $CO_F$ is inversely related to ventilation; our normal range is 42·2% to 61·5%.

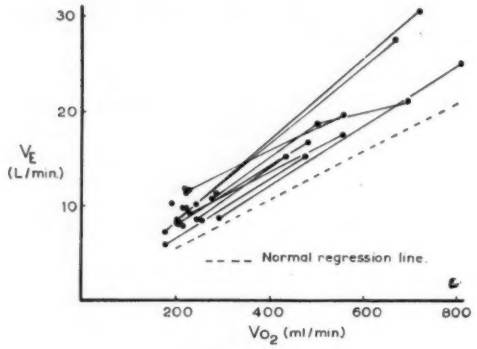


FIGURE I

The ventilation ($\dot{V}_E$) of 19 patients with emphysema and its rise with exercise. In this and the next two figures the regression lines shown are those found previously in this laboratory (Holland and Blacket, 1958.) ($\dot{V}O_2$: oxygen consumption)

*Diffusing Capacity*

Diffusing capacity was lowered in all cases (Table II). The mean resting value was 7·2 ml./min./mm. Hg. The standard deviation was 2·1 ml./min./mm. Hg, but, as the frequency distribution of values for $D_{CO}$ was skewed, this

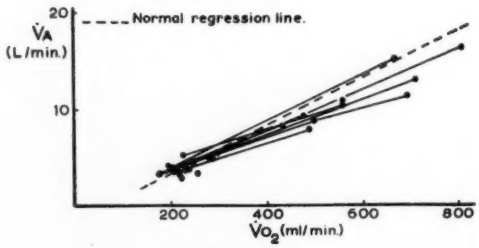


FIGURE II

The alveolar ventilation ($\dot{V}_A$) in 19 cases of emphysema and its rise with exercise

does not give a true estimate of scatter. The mean in a younger group of normal subjects in this laboratory was 22 ml./min./mm. Hg (Holland and Blacket, 1958). $D_{CO}$ rose with exercise in all cases, but did not reach normal values.

The rise is shown in Figure III. The rise usually ran approximately parallel to the regression line for normal subjects. $D_{CO}$ was plotted against R.V./T.L.C. for different values of M.B.C., and against $V_D(C)/V_T(C)$ (Figures IV and V). No correlation with any of these was found. As far as $D_{CO}$ reduction could be compared with disability, little correlation was noted. Patient A.D., with the lowest $D_{CO}$, was bedridden, but he had anæmia, which contributed both to $D_{CO}$ lowering and to his disability. Patient G.C.S., with a resting $D_{CO}$ of 5·9, was able to do sedentary work and light exercise without undue distress; while patient S.F., with a resting $D_{CO}$ of 9·8, was distressed on the slightest effort.

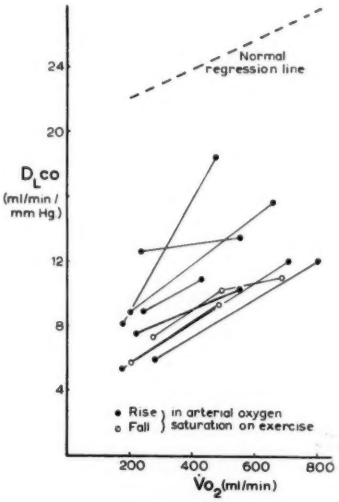


FIGURE III

The diffusing capacity of patients with emphysema and its rise with exercise. The patients who did not exercise are not shown

## DISCUSSION

The patients of this study form a selected group of patients with chronic obstructive lung disease. No patients with carbon dioxide narcosis were studied. Very mild cases were also excluded. We have seen several patients with the clinical features of "emphysema" without any increase in the ratio R.V./T.L.C. or reduction of M.B.C. Their disability was not severe. Because of the uncertainty of diagnosis, we have omitted such cases from this paper.

In comparing this with other reported series, it is necessary to consider the comparative severity of the cases, and also the essential technical differences between the methods used for estimation of diffusing capacity.

### *Back Tension of Carbon Monoxide*

Neglect of the tension of carbon monoxide in equilibrium with carboxyhæmoglobin in the pulmonary capillaries can cause significant underestimation of $D_{CO}$ in normal subjects (Linderholm, 1957; Holland and Blacket, 1958).

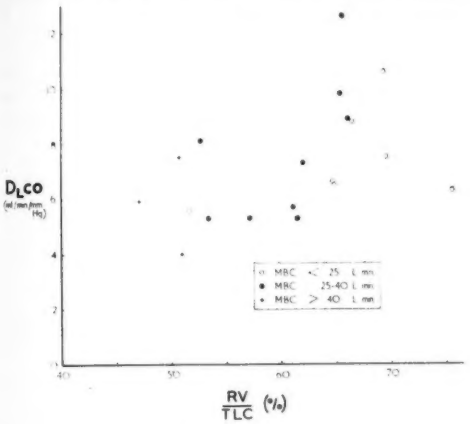


FIGURE IV

The relation between diffusing capacity and the ratio of residual volume to total lung capacity in cases of emphysema. Note the absence of correlation

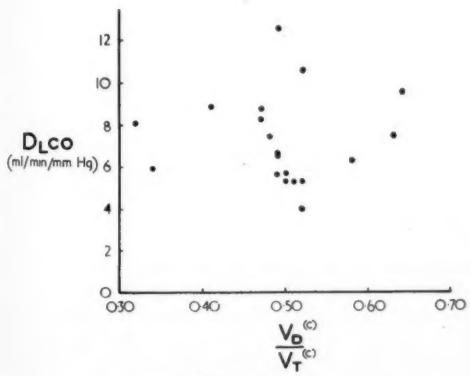


FIGURE V

The relation between diffusing capacity and the ratio of dead space to tidal volume in cases of emphysema. There is no correlation

This is less important in the Hamman-Rich syndrome (Holland and Blacket, 1960), and for the same reasons the error is less serious in the cases reported here than in normal subjects. Carbon monoxide uptake is less, and so there is less build-up of carboxyhæmoglobin in the course of the estimations. Also, the alveolar carbon monoxide tension is relatively higher, as can be seen from comparing the ratio of alveolar to inspired carbon monoxide in Table II with the usual finding of a ratio less than 0·25 in resting normal subjects. This higher alveolar tension also lessens the effect of carboxyhæmoglobin present before the start of the test. Other factors which lessen back tension are the decreased oxygen tension and increased amount of reduced hæmoglobin in the pulmonary capillaries in cases of diffusion defect. If the amount of reduced hæmoglobin is significant, the back tension decreases and is impossible to estimate accurately (Forster *et alii*, 1957; Roughton and Forster, 1957).

To confirm the impression that back tension is not of great importance, it was measured in patient S.F. Carboxyhæmoglobin was measured by the method of Roughton and Root (1945), and the $D_{CO}$ was corrected for this as described by Linderholm (1957). The correction was from 9·0 to 9·8 ml./min./mm. Hg. In this case, the ratio of alveolar to inspired carbon monoxide was one of the lowest of the series, so the correction was larger than would apply in many cases. Thus, although neglect of carboxyhæmoglobin does cause an error, it is not great, and cannot be held accountable for the lowering of $D_{CO}$ in these cases, particularly as in the normal subjects used for comparison (Holland and Blacket, 1958), no correction was made for back tension.

### *Severity of the Disease*

The severity of the disease is shown by the high values for the ratio R.V./T.L.C.; the series is comparable with Groups II and III of Baldwin *et alii* (1949*b*). It is more difficult to compare them with respect to M.B.C., as the results of Baldwin *et alii* are expressed as percentages of predicted values and they used different standards. On the other hand, the frequency with which the arterial oxygen saturation rose on exercise to values above 92% places many of the cases in their Group I. The mean value of the ratio R.V./T.L.C. in the emphysematous patients of Marshall (1958) was 60%, virtually identical with that in the present series. The values for R.V./T.L.C. and M.B.C. are similar to those in the cases reported by Ogilvie (1959). The patients of Shepard *et alii* (1955) were selected for their ability to exercise, and so were less severely affected than ours. The cases were approximately comparable to those of Lewis *et alii* (1959), and were, on the whole, a little less severe than those of Williams and Zohman (1959). Insufficient data were available to compare the series of Kjerulf-Jensen and

Kruhøffer (1954), of Bates *et alii* (1956), and of MacNamara *et alii* (1959). In the cases of Ogilvie and Catterall (1959) bullæ were the primary abnormality, and for this reason no comparison will be attempted.

### *Comparison of Methods of Measurement of Diffusing Capacity*

The basis of the various methods was examined by Forster (1957). He pointed out that no method gives the true value for pulmonary diffusing capacity, and this makes comparisons difficult. In emphysema and airway obstruction certain errors are likely to arise, and these are considered below.

The steady-state carbon-monoxide method of Bates, Boucott and Dormer is not suitable for use in emphysema. It is subject to error for the same reason as in the Hamman-Rich syndrome (Holland, 1960; Holland and Blacket, 1960)—namely, that the large physiological dead space renders invalid the use of an assumed dead space or end-tidal sampling in the estimation of alveolar carbon monoxide tension. Moreover, Marshall (1958) showed that in emphysema, the expired alveolar carbon monoxide concentration changes considerably during the expiration.

The steady-state physiological dead-space method of Filley *et alii* for $D_{CO}$ is less subject to errors caused by ventilatory inequalities in the lung. In the calculation, over-ventilated regions appear to a large extent as increase in physiological dead space, and so do not cause so great an over-estimation of alveolar carbon monoxide tension. The precise importance of these inequalities depends on the rate of perfusion of the different alveoli, and there is no way of knowing this. The result of the aforementioned inequality is to cause an under-estimation of $D_{CO}$. However, the use of arterial carbon dioxide tension in the estimation of physiological dead space tends to over-estimate $D_{CO}$. The net effect is probably an under-estimation of $D_{CO}$, but to a less extent than in the Bates method. In emphysema, the alveolo-capillary membrane is not thickened, and so there is no variation in the ratio of diffusing capacity to physiological alveolar ventilation caused by variations in the thickness of the alveolo-capillary membrane throughout the lung.

In the modification of the Filley method described by Marshall (1958), arterial puncture is not required. The mixed venous carbon dioxide tension is measured by a rebreathing method after the measurement of carbon monoxide uptake. By assuming values for cardiac output and for arterial and venous pH, a value for end-capillary carbon dioxide tension can be calculated. The use of end-capillary rather than arterial carbon-dioxide tension in the calculation of dead space eliminates errors due to anatomical shunts, and should give a lower value for both dead space and diffusing capacity. The assumption of pH values and cardiac output makes the possible errors of this method hard to assess. However, the use of a value for carbon-dioxide tension not measured during the period of carbon monoxide uptake is open to question, as the ventilatory pattern of these patients is very variable and the values for arterial carbon dioxide tension in the two periods may not be the same; for example, the resting arterial carbon dioxide tension of patient A.F. of the present series fell considerably when he was connected to the valves.

The breath-holding method of Krogh (1915) as modified recently (Forster *et alii*, 1954; Ogilvie *et alii*, 1957; Curtis *et alii*, 1958*a*) is liable to error for two reasons. First, if the sample expired contains air from different diffusing phases (that is, if the ratio of diffusing capacity to alveolar volume ($D_L/V_A$) is not uniform throughout the regions contributing to the expirate), the $D_{CO}$ obtained is an underestimate. This is due to the excessive weighting of the result by those regions where $D_{CO}$ is low. However, the error introduced in this way is not very great. The second source of error is difference in the ratio $D_L/V_A$ between those regions of the lung which contribute to the sample and those which do not. In the calculation of single-breath $D_{CO}$, the equation for the exponential fall in alveolar carbon monoxide concentration is solved, by the use for the final alveolar carbon monoxide concentration of the value for carbon monoxide in the expired sample after the first portion has been discarded. The solution gives the value for $D_L/V_A$. Diffusing capacity is then calculated by means of a value for alveolar volume obtained from the spirographic record of the breath and the residual volume independently determined. In diffuse airway obstruction, the chances of the expired sample being unrepresentative are increased. If the expired sample is derived from those parts of the lung which have a better diffusing capacity, the $D_{CO}$ will be over-estimated. The error will be increased if, as is likely in obstructive airway disease, the volume of air expired as a sample is relatively small when compared with the total lung capacity. A calculation of the extent to which this can cause error has been made by Lewis *et alii* (1959).

Another source of systematic difference between the breath-holding and steady-state methods may be the greater lung volume at which the single-breath estimations are made. Ogilvie *et alii* (1957) found little change in $D_{CO}$ with lung volume; but other workers (Marks *et alii*, 1957; Marshall, 1958; Mittman and Burrows, 1959) have confirmed to a greater or lesser extent the original observation of Krogh (1915) that $D_{CO}$ increased significantly with lung volume. Marshall (1958) was able to explain all the difference between breath-holding $D_{CO}$ and steady-state $D_{CO}$ in a group of normal subjects by the greater lung volumes at which the former estimations were made.

It is difficult to know the effect of non-uniformity on the estimation of diffusing capacity by the two-level oxygen method of Riley *et alii* (1951, 1954). Forster (1957) considers that some under-estimation is the likely net effect. Similarly, it is hard to know the effect of non-uniformity in the rebreathing method of Kruhøffer (1954). Although this method was designed to achieve uniformity in the lung, it is unlikely that patients with a large, poorly-ventilated space and a low M.B.C. can achieve the desired degree of mixing between all parts of the lung and the external bag. One disadvantage of the rebreathing method is the ventilatory effect involved; true resting values cannot be obtained, and the exact amount of exercise done by the respiratory muscles is not known. Moreover, hyperventilation itself may raise the $D_{CO}$.

Non-uniformity is characteristic of obstructive lung disease and was present in this series. Its effect cannot be estimated exactly, but information can be gained by an examination of the results.

### *Increase in Physiological Dead Space*

Increase in physiological dead space can be caused by increase in anatomical dead space or by inequalities in the ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}_c$). Increased anatomical dead space has been demonstrated in old age and in obstructive lung disease (Fowler, 1950; Tenney and Miller, 1956; Wilson *et alii*, 1957). Tenney and Miller found an increase in anatomical dead space in a group of persons of mean age 78 years. Fowler found a small increase in anatomical dead space in a group of men of mean age 60 years—similar to the mean age of the present series. There was a small further increase in anatomical dead space in the group with emphysema whose mean age was 66 years, but the figures Fowler found for anatomical dead space were well below the physiological dead space of our series. In all our cases the ratio $V_D(C)/V_T(C)$ was raised, and its mean value was close to that found by Wilson *et alii* in cases of obstructive lung disease of similar mean age. They measured anatomical dead space and found a mean value of 203 ml., which is 30 ml. below our mean physiological dead space. However, the mean physiological dead space in their series was 333 ml., indicating inequalities in the ratio $\dot{V}_A/\dot{Q}_c$. Thus the increase in dead space in our series is regarded as largely due to inequalities in this ratio. Alveoli with high values for $\dot{V}_A/\dot{Q}_c$ are more important in raising the dead space than are alveoli with low values (Severinghaus and Stupfel, 1957) so the presence of excessively ventilated regions is inferred. The effect of this form of non-uniformity is much less in the Filley method than in the Bates method; the use of physiological dead space largely compensates for the differences in ventilation in the lung.

### *Other Evidence of Non-Uniformity*

There were other manifestations of non-uniformity in this series. Delay in intra-pulmonary mixing of helium showed non-uniformity of the ventilation with respect to the lung volume—that is, non-uniformity in the gaseous phase of the lung. The raised physiological dead space and increased venous admixture are expressions of non-uniformity of the ventilation-perfusion ratio. Similarly, the lowering of the arterial oxygen saturation out of proportion to the diffusion defect, and the improvement in the arterial oxygen saturation on exercise in some—a sign that the increased ventilation on effort is reaching regions which were poorly ventilated at rest—are expressions of ventilation-perfusion imbalance. However, it is not possible to know the degree of non-uniformity of the ratio of diffusing capacity to physiological alveolar ventilation, which is important in the steady-state methods of measuring diffusing capacity.

### *Values Found for $D_{CO}$*

The values found for $D_{CO}$ varied from slight reduction (patient G.S.) to extreme reduction (patient A.D.). The failure of $D_{CO}$ reduction to correlate with increase of the ratio R.V./T.L.C. and decrease of the M.B.C. is not surprising, as $D_{CO}$ is a measure of available alveolo-capillary surface area, while the other tests are primarily of airway obstruction. Shepard *et alii* (1955) also found no correlation between reduction of diffusing capacity and the results of tests of obstruction. Similarly, since the symptoms in

this condition are usually due to airway obstruction and other mechanical disorders, the failure of $D_{CO}$ reduction to correlate with disability was only to be expected.

The rise of $D_{CO}$ on exercise may have been due to the opening up of fresh capillaries, to improved uniformity, or to decreased intracapillary resistance to carbon monoxide uptake associated with the lowering of the mean pulmonary capillary oxygen tension on exercise. These factors may well have operated together, but the relative importance of each is not known. In three cases the results point to improvement in uniformity as an important factor. In patient's C.B., F.R. and G.C.S., the $D_{CO}$ more than doubled at comparatively low oxygen consumptions; a doubling is not seen in normal subjects until heavy exercise is undertaken (Holland and Blacket, 1958). In each of the abovementioned three subjects the oxygen saturation also rose, thus indicating an improvement in uniformity of the ratio $\dot{V}_A/\dot{Q}_c$. Some of the rise in $D_{CO}$ is attributed to improvement in uniformity. This implies false lowering of resting $D_{CO}$ in some cases.

The severe lowering of $D_{CO}$ in the series, both at rest and on exercise, is probably due both to anatomical factors—loss of alveolo-capillary surface area—and to non-uniformity of ventilation and perfusion. Decrease in pulmonary capillary blood volume ($V_c$) may have played a part in $D_{CO}$ reduction in some cases, but McNeill *et alii* (1958), who measured it in association with the single-breath $D_{CO}$ in three cases of obstructive lung disease, found no reduction of $V_c$ in any case. No measurements of pulmonary capillary blood volume in this condition have been made in association with steady-state $D_{CO}$ studies.

*Comparison with the Findings of Others*

The only other series of cases of obstructive lung disease studied by the Filley $D_{CO}$ technique is that described recently by Williams and Zohman (1959). Our general findings are very similar to theirs. They found resting $D_{CO}$ reduced in all cases, sometimes very severely, despite the mean cardiac index being normal. A rise on exercise occurred in all but one case, the rapidity of the rise showing considerable variation from case to case. Also, they found no correlation between hypoxæmia and reduction of diffusing capacity. They consider that the lowering of diffusing capacity is due to true loss of alveolo-capillary surface rather than to non-uniformity caused by airway obstruction. In support of this is their finding of little reduction of $D_{CO}$ in cases of bronchial asthma (Williams and Zohman, 1960). Lewis *et alii* (1959) found that the Filley method gave much lower results than the rebreathing method in two out of three cases of "emphysema". "Rebreathing" $D_{CO}$ was rarely less than two-thirds of the predicted value, whereas the Filley $D_{CO}$ was as low as 5 ml./min./mm. Hg in one case. Kjerulf-Jensen and Kruhøffer (1954) also found little reduction in rebreathing $D_{CO}$ in clinically severe cases. Lewis *et alii* consider that the rebreathing method is more likely to give the true answer than is the steady-state technique; but in their model lung calculations they used a fixed dead space of 150 ml. The higher dead spaces actually found when the Filley method is used would result in an increase of $D_{CO}$. The extent to which this occurs depends on distribution of blood flow with respect to ventilation and diffusion, and little is known of this at present. Marshall (1958) found little reduction in $D_{CO}$ in an apparently comparable series, using his modified Filley method. No explanation can be offered for this. The one patient studied by Forster *et alii* (1955) by the Filley method had a higher $D_{CO}$ than any of our patients, but one of the duplicates was impossibly high and the figures cannot be accepted as reliable.

The presence of a raised physiological dead space in obstructive lung disease means that the values for $D_{CO}$ of Bates, Knott and Christie (1956) and of MacNamara *et alii* (1959), both using the method of Bates, Boucott and Dormer (1955), are likely to be falsely low. The findings of the former, that $D_{CO}$ failed to rise on exercise, are contrary to our findings and to those of MacNamara *et alii*, but we cannot suggest any explanation of this.

The resting values for $D_{CO}$ in our series were of the same order as the value for $D_{O_2}$ found in the more severe cases of emphysema by Donald *et alii* (1952) using the two-level oxygen method of Riley *et alii* (Riley *et alii*, 1951, 1954). They stressed the importance of disparity in ventilation-perfusion ratios in causing an apparent reduction in alveolo-capillary surface. Exercise $D_{CO}$ in the present series was more reduced than was $D_{O_2}$ in the cases of Shepard *et alii* (1955), who measured "maximal diffusing capacity", but most of their patients were able to exercise harder than ours.

Many of the studies of $D_{CO}$ in obstructive lung disease have been made by the modification of the breath-holding method described by Ogilvie *et alii* (1957). They found $D_{CO}$ severely reduced in a few patients, but near to the lower limit of normal in others. Marshall (1958), in an apparently comparable series, found $D_{CO}$ considerably higher than in our cases. The mean $D_{CO}$ in the cases of Curtis *et alii* (1958*b*)

was also higher, and $D_{CO}$ reduction was only slight in the three cases of emphysema studied by McNeill *et alii* (1958). Lewis *et alii* (1959) compared the rebreathing $D_{CO}$ with the breath-holding $D_{CO}$ in nine cases of emphysema. The values obtained by the two methods were approximately the same, showing little reduction of $D_{CO}$.

Ogilvie (1959) found $D_{CO}$ less reduced in cases of emphysema with a long history of chronic bronchitis than in those without such a history. He suggested that there were two factors concerned in pathogenesis — one associated with chronic bronchitis, which can produce the clinical and physiological picture of emphysema and cor pulmonale without detectable damage to the alveolar and capillary tissues of the lung, and another in which " centrilobular " inflammation leads to actual destruction of respiratory tissue (Leopold and Gough, 1957).

The present series is not a suitable one for examining this point as almost all the patients had long-standing bronchitis. However, Mrs. C.B., a non-smoker, aged 65 years, had never had symptoms of chest disease of any kind until she became breathless at about the age of 60 years. She fits well into a hypothetical group without primary bronchial obstruction. We agree, too, with Ogilvie that chronic bronchitis and, incidentally, chronic asthma may both cause prolonged incapacity, cor pulmonale and death without permanent impairment of the diffusing capacity. That this is so emphasizes the difficulty in making during life the pathological diagnosis of emphysema, even though the clinical signs are indubitable.

Until pathological evidence becomes available, we cannot accept that the differences in diffusing capacity, as determined by the breath-holding technique on Ogilvie's patients studied in London and by the Filley steady-state method on our patients in Sydney, are real.

The higher values with the breath-holding technique are partially explicable on the basis of their measurement at higher lung volumes, and perhaps more importantly, by the delivery of a non-representative sample.

In general, reduction of $D_{CO}$ in emphysema is less important in contributing to symptoms than the impairment of the " bellows " action of the chest. But in some cases the low $D_{CO}$ must surely be significant. Uneconomic ventilation due to the raised physiological dead space is another factor which contributes to dyspnœa in some cases. Many studies over a long period will be necessary before the symptoms and physiological aberrations can be reconciled with the pathology.

## ACKNOWLEDGEMENTS

We are indebted to Mrs. G. Anderson, Mr. D. Fahey, Mr. P. Donnelley and Miss D. Warren for technical assistance. Photographs of the illustrations for reproduction were prepared in the Department of Illustration, University of Sydney. One of us (R.H.) was supported in part by the Marion Clare Reddall Scholarship, the Anderson Stuart Memorial Research Fellowship and the Joseph Goodburn-Smith Research Fellowship while the work was carried out.

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# MAXIMAL EXPIRATORY FLOW RATES IN AUSTRALIAN ADULTS[1]

T. SELBY[2] AND JOHN READ[3, 4]

*From the Department of Medicine, University of Sydney,[4] and the Pulmonary Clinic, Sydney Hospital, Sydney*

SUMMARY

The Wright peak flow meter is a useful, simple, portable instrument for the recording of maximal expiratory flow rates (M.E.F.), which reflect the degree of obstruction to air flow.

Normal values for M.E.F. under Australian conditions have been determined in 44 males and 76 females, aged 18 to 78 years, who had no history of chronic respiratory disease and who had never smoked. Regression equations have been prepared for the prediction of " normal values " in practice. In normal subjects, the recorded M.E.F. may vary from the predicted value by up to 20%. In 10% of the subjects, the reproducibility of the test was not good.

Increasing age is associated with loss of M.E.F. in both sexes (for males 2·1 litres per minute, and for females 1·2 litres per minute, each year). In males, stature (as reflected by height) is important as a determinant of the absolute value for M.E.F.

In women over the age of 60 years, three determinations are adequate to achieve a maximum value, but in younger women at least four determinations and in men at least five determinations should be made.

THE commonest cause of respiratory disability is interference with the ventilatory (or " bellows ") function of the lungs. This disability is in turn most commonly due to organic or functional airway obstruction—the disturbance seen in asthma, bronchitis and emphysema.

Expiratory airway obstruction unduly limits the rate at which air can be forcibly expelled from the lungs, and this relationship is utilized in several formal tests of ventilatory function. In the best-known test, the tracing produced by forced expiration of the vital capacity into a spirometer recording on fast-moving paper is studied (forced expiratory volume or F.E.V. over various time intervals). From such a tracing, the maximum breathing capacity (M.B.C.) can also be adequately predicted; or indeed, at the cost of additional effort by subject and operator, the M.B.C. may be directly measured with the same spirometer.

The major disadvantages of such apparatus are its bulk, relative immobility and cost. These disadvantages have been overcome by the introduction of the Wright peak flow meter[5] (Wright and McKerrow, 1959). Using this instrument (Figure I), the subject takes a maximal inspiration, places the mouthpiece in his mouth, and blows as hard as he can. He is not required to empty his lungs, for the needle on the face of the instrument records the peak rate of air flow achieved for 10 milliseconds or more, and this peak always occurs early in expiration. Reduction of peak flow rate below normal implies increased airway obstruction,

FIGURE I

and the degree of reduction provides an objective measure of the severity of obstruction. Higgins (1957) demonstrated a close correlation between peak expiratory flow rate measured with a pilot version of this instrument and maximum breathing capacity.

" Normal values " for use with the instrument have been derived for adults in South Wales (Higgins, 1957) and Scotland (Lockhart *et alii*, 1960). Since other parameters of ventilatory

[1] Received on November 10, 1960.

[2] Honorary Clinical Assistant, Pulmonary Clinic.

[3] Senior Lecturer in Medicine; formerly Assistant Physician in Charge of Pulmonary Clinic.

[4] Supported by grants from the National Health and Medical Research Council, the Joint Coal Board, the Post-Graduate Medical Foundation, and the Consolidated Medical Research Fund of the University of Sydney.

[5] Airmed Ltd., Harlow, England.

function have been found to vary from country to country, it seemed useful to obtain values for use under Australian conditions.

## MATERIALS AND METHODS

Adult subjects were studied in the out-patient department of Sydney Hospital. They consisted of males and females, aged 18 years or more, in the following categories: (i) Ambulant out-patients waiting to be examined at general surgical, gynæcological, urological, neurosurgical, orthopædic and dermatological clinics. General and special medical clinics were specifically avoided. (ii) Friends waiting with patient. (iii) Members of the medical, nursing, almoner and clerical staff of these clinics.

Subjects were not accepted for this study of normal values if they fell into one of the following categories: (i) they had a history of bronchial asthma or recurrent bronchitis; (ii) they had any cough or sputum; (iii) they had ever regularly smoked more than one cigarette per day.

The subjects thus consisted of ambulant, non-"medical" out-patients, their friends and attendants, who had never smoked a significant amount of tobacco and who had no symptoms or history of bronchitis or asthma. There were 44 males, aged 18 to 74 years, and 76 females, aged 21 to 78 years. Age, height and weight were recorded in every case.

The procedure was carefully explained to each subject, who carried it out five times. Thus five maximal expiratory flow rates (M.E.F.) were recorded for each subject.

Standard statistical methods were used for calculation of regression equations, confidence limits and correlation coefficients.

## RESULTS

### *Prediction of Normal Values*

The best value for M.E.F. from five attempts was considered for each subject. Multiple correlation coefficients were calculated, and

TABLE I

*Best Regression Equations for Prediction of M.E.F.*

| Group | Regression Equation M.E.F. (L./min.)[1] | $r$ | $P$ | 95% Confidence Limits (L./min.) |
|---|---|---|---|---|
| Males (44) | 3·2H−2·1A+71 | 0·659 | <0·001 | ±114 |
| Females aged up to 60 years (56) | 452 −1·2A | −0·271 | 0·05 | ±103 |
| Females aged over 60 years (20) | 598B−670 | 0·744 | <0·001 | ±103 |

[1] H, height in centimetres; A, age in years; B, body surface area in square metres.

regression equations prepared, relating M.E.F. to (*a*) age, (*b*) age and height, (*c*) age and weight, (*d*) age and body surface area, (*e*) age, height and weight, for each sex separately.

The best predictions of M.E.F. were given by the regression equations shown in Table I. Females had to be considered in two separate age groups, since the pattern of performance seemed to change at about 60 years.

### *Value of Repeating Procedure*

Table II shows on which occasion out of the five efforts the highest M.E.F. was first recorded. Among men, more than half improved up to the fourth or fifth attempt. Among women aged under 60 years, more than two-thirds had done their best after the third attempt. Table III indicates the underestimates of M.E.F. which

TABLE II

*First Occasion (out of Five Expirations) on which Best Value of the Five was Recorded*

| Subjects | Expiration with Best Value First Recorded | | | | |
|---|---|---|---|---|---|
| | First | Second | Third | Fourth | Fifth |
| Males | 3 | 4 | 9 | 15 | 13 |
| Females (up to 60 years) | 7 | 11 | 21 | 8 | 9 |
| Females (over 60 years) | 4 | 9 | 5 | 1 | 1 |

would have been introduced by recording only three or four M.E.F.'s instead of five. If underestimates of less than 20 litres per minute are disregarded, it appears that three determinations are adequate in women aged over 60 years, and four in women aged under 60 years, but that five determinations are necessary in men.

TABLE III

*Underestimates of M.E.F. Introduced by Omitting Fifth or Fourth and Fifth Attempts*

| Group | Number of Subjects | Total Underestimates | Size of Underestimates (L./min.) | | |
|---|---|---|---|---|---|
| | | | 1–20 | 21–40 | 41–60 |
| Fifth attempt omitted | | | | | |
| Males | 44 | 13 | 11 | 1 | 1 |
| Females (<60) | 56 | 9 | 9 | — | — |
| Females (>60) | 20 | 1 | 1 | — | — |
| Fourth and fifth attempts omitted | | | | | |
| Males | 44 | 28 | 16 | 9 | 3 |
| Females (<60) | 56 | 17 | 13 | 4 | — |
| Females (>60) | 20 | 2 | 2 | — | — |

The first attempt may well be regarded as a "practice run", and indeed most subjects treat it as such. Despite this, 50% of the men and 60% of the women achieved an M.E.F. within 10% of their best recorded value on the first attempt at the test.

### *Reproducibility of Serial Values*

One hundred and eight subjects (90%) produced at least three values at five attempts which were within 10% of the maximum recorded value. In the other 12 subjects (10%), three values out of the five were more than 10% below the maximum recorded value.

All comparisons with "best value" among these results presuppose that the maximal possible value was indeed recorded among the first five. This assumption is based on practical expediency, and indeed, patient cooperation

tends to fall off after five attempts. The frequency distributions of the results in Table II in fact suggest that a significant number of better results may have been obtained on sixth or seventh attempts among males particularly.

## DISCUSSION

In two years of personal use, the Wright peak flow meter has proved a useful screening tool in the wards, the out-patient department and the laboratory. Similar impressions of its value have been recorded from overseas (Higgins, 1957; Wright and McKerrow, 1959; Lockhart *et alii*, 1960; Fletcher, 1960). A significant number of these instruments have been acquired by institutions and individual clinicians in Australasia, and it was thought that diagnostic precision in borderline situations would be improved by the establishment of local standards of "normality".

The subjects in the present study are not a random population sample, but it is suggested that they compare more than favourably with most groups hitherto used for the establishment of "normal" standards for parameters of respiratory function. The use of "non-medical" out-patients obviates many of the objections to the use of hospital patients. The criteria laid down for acceptance into the group were rigid compared with usual standards—not only the absence of cough, sputum and any history of asthma or recurrent bronchitis, but also the absence of any significant past or present tobacco smoking. The exclusion of smokers and ex-smokers limited the number of subjects available for study, but increased confidence in the respiratory "normality" of the group. Analysis of the present results separately for patients, friends and staff (see materials and methods) revealed identical mean values for patients on the one hand and friends and staff on the other in each sex and age group.

Both males and females showed a significant loss of M.E.F. with increasing age (Table I). In men, this amounted to 2·1 litres per minute each year. The loss in women (1·2 litres per minute each year), while statistically significant, is barely biologically so. The importance of differences of climate, atmospheric pollution and geography is seen in a comparison of these losses with those in a South Wales agricultural population (Higgins, 1957), where males lost 6·3 litres per minute and females 3·8 litres per minute each year. The present results are rather closer to those reported from Scotland by Lockhart *et alii* (1960).

Though airway obstruction has been emphasized as the major factor reducing the M.E.F., it will be apparent that the size of the chest and the stature and strength of the subject may play a considerable part in determining the absolute value recorded. It was for this reason that the various physical attributes of height, weight and body surface area were considered. Height allowed the best prediction of M.E.F. in men—each centimetre increase in height led to an increase of 3·2 litres per minute of M.E.F. Thus a difference in height of 6 in. between two men of the same age implies a difference of nearly 50 litres per minute in M.E.F. Height is also the principal physical determinant of differences in vital capacity (Needham, Rogan and McDonald, 1954). Only in later life does one of the physical attributes (body surface area) become significant among females.

The normal range (last column, Table I) at first sight appears wide. In terms of absolute values, it represents a range of about ±20% around the means. This range is of the same order as that seen in determinations of the vital capacity (Holmes, 1959).

The reproducibility in a single series of determinations was not quite as good as has been claimed by some (Lockhart *et alii*, 1960). Ten *per centum* of the subjects failed to produce three values out of five within 10% of their maximum recorded value. It cannot therefore be stated that malingerers can be detected with confidence because of their inability to reproduce consistent values. In this respect, the test must be regarded as inferior to graphic recording of the forced expiratory volume, in which the conscious efforts of the malingerer can be readily seen. On the other hand, the overall simplicity of the test is illustrated by the fact that 50% to 60% of the subjects recorded an M.E.F. within 10% of their maximum at their first attempt.

From Table III it would seem that at least five determinations should be made in men, at least four in women aged under 60 years, and at least three in women aged over 60 years.

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# LIVER INVOLVEMENT IN "Q" FEVER[1]

O. W. POWELL[2]
*From the Princess Alexandra Hospital, Brisbane*

SUMMARY

In 72 consecutive cases of "Q" fever, hepatomegaly occurred in 47, and jaundice in three.

Abnormal results for serum cephalin-cholesterol flocculation, thymol turbidity or serum alkaline phosphatase activity were found in 61 cases. The test that most commonly produced an abnormal result was the cephalin-cholesterol flocculation test (56 cases); this was followed by the serum alkaline phosphatase estimation (26 cases) and the thymol turbidity test (25 cases). During the first four weeks, the serum alkaline phosphatase level was related to the degree of cephalin-cholesterol flocculation. Positive cephalin-cholesterol flocculation commonly persisted for several months.

Increased serum alkaline phosphatase levels were frequently the first, and occasionally the only, biochemical evidence of liver involvement. Quite high values were seen at times.

Serum transaminase activity was only moderately increased, even in jaundiced patients.

Liver biopsy was performed on 13 patients of the series, and on an additional jaundiced patient admitted to hospital subsequently. The predominant histological pattern was one of focal inflammation. This was of all grades, from small collections of mixed inflammatory cells to frank granulomas with central necrosis and fibroblastic reaction. In one patient a focal inflammatory lesion was found in the liver 17 weeks after the onset of the illness.

JAUNDICE was a feature of one of the nine cases of "Q" fever originally described by Derrick (1937); but subsequent reports laid more emphasis on the pulmonary features of the illness (Hornibrook and Nelson, 1940; Lillie *et alii*, 1941; Finland and Dingle, 1942), although the second-named authors mention the morphological changes in the liver in a fatal case. In reporting an epidemic amongst troops in the Mediterranean area, Robbins and Ragan (1946) found no jaundice amongst 374 cases, and stated that "hepatomegaly did not occur". In a survey of 80 cases in California, Denlinger (1948) found hepatomegaly in three only, and no jaundice. Subsequently, however, Clark *et alii* (1951) found hepatomegaly in 11% and jaundice in 5% of 180 cases. Further reports of jaundice appeared from time to time, notably from Switzerland (Ludwig, 1956; Wespi, 1957), and Italy (Schiavina and de Stefanis, 1951). In 1958 Douglas described four cases in northern Queensland, and emphasized the importance of jaundice in the differential diagnosis of infective hepatitis.

Apart from the autopsy mentioned above, there appear to have been no reports of abnormal liver morphology in human "Q" fever until 1956, when Gerstl *et alii* described their findings in four patients submitted to needle biopsy. These revealed foci of hepatocellular damage with infiltration of round cells, eosinophils and occasional neutrophils and histiocytes. They commented that the scarcity of inflammatory cells and the absence of fibroblasts set them apart from true granulomas. They believed that the lesions were of short duration. They briefly mentioned the results of some liver function tests on these patients. Finally, Tonge and Derrick (1959) detailed their findings in a patient with "Q" fever hepatitis who died five days after a laparotomy, performed to determine the cause of his jaundice. In this patient there was widespread liver-cell necrosis.

One other paper of interest is that by Hicks *et alii* (1948), who, in an investigation into the influence of fever upon various liver-function tests, demonstrated the appearance of abnormal flocculation in a high proportion of cases of "primary atypical pneumonia" in the Italian theatre of war. As the authors point out, writing in retrospect, many of these were undoubtedly examples of undiagnosed "Q" fever.

There seems to have been no systematic study of the incidence and extent of liver involvement in "Q" fever. During the course of a clinical study of the disease as it appears locally, it was decided to pay particular attention to this aspect, and to the behaviour of a variety of liver-function tests, supplemented by needle biopsy as opportunity offered.

[1] Received on July 8, 1960.
[2] Medical Superintendent.

## MATERIAL

This is a consecutive series of 72 patients with "Q" fever admitted to the public wards of this hospital between July, 1958, and June, 1959, apart from two short periods in December and April. Reference will also be made to two patients admitted outside this period, and not included in the series. Criteria for diagnosis, symptomatology and findings on physical examination have been given previously (Powell, 1960).

Hepatomegaly was detected in 47 of the series (65%), and tenderness below the right costal margin was present in eight patients (11%) in whom no liver enlargement could be demonstrated. Jaundice occurred in three patients. The spleen was palpable in 38 of the group (53%).

The following investigations were performed as a routine procedure on all patients on their admission to hospital and at intervals during the illness and convalescence: serum bilirubin estimation, serum alkaline phosphatase estimation (King-Armstrong units), cephalin-cholesterol flocculation test (48-hour reading) and thymol turbidity test. Estimation of bromsulphalein retention (5 mg. in 45 min.) was carried out on the majority. In the earlier cases, serum glutamic oxalacetic transaminase activity was estimated on samples of frozen sera sent to the Walter and Eliza Hall Institute. Later, after a period when no such estimations were done, this was estimated in our own laboratory. Needle biopsy was performed on 13 patients in the series at different stages of the illness, and on one additional jaundiced patient who is not otherwise included in the series.

All 72 patients were male. The age incidence was as follows: 19 years or less, 22; 20 to 29 years, 15; 30 to 39 years, 14; 40 to 49 years, 9; 50 to 59 years, 9; 60 to 69 years, 2; 70 years or more, 1. The youngest patient was aged 14 years, and the oldest 70 years.

## INVESTIGATIONS

### *Serum Bilirubin Estimation*

Serum bilirubin levels above 1·0 mg. per 100 ml. were found in only five patients, of whom three were jaundiced. The highest level observed was 7·3 mg. per 100 ml., but in one patient who has been seen since then, a level of 12·6 mg. per 100 ml. was reached (G.H.—see later).

### *Flocculation Tests*

Only one of 48 patients seen before the seventh day had a cephalin-cholesterol flocculation of "+++" or "++++" By the end of the tenth day the proportion had risen slightly, to five out of 58 cases. However, in the period from then until the end of the third week the incidence of positive results ("+++" or "++++") rose sharply to 55% of the 60 patients tested, and in the fourth and fifth weeks the incidence reached 76% of the 59 patients examined in that period. Thereafter the incidence decreased as the result of the test returned to normal. Nevertheless, positive results were obtained in quite a high proportion at eight weeks. The longest period over which the result of the test remained positive was 165 days. In all, 56 patients (78%) developed "+++" or "++++" flocculation at some stage.

Abnormal values for thymol turbidity were not seen in the first ten days, but in the period from then until the end of the third week 16 of the 60 patients tested had levels of 6 units or more. In the following two-week period this proportion had risen to 19 of the 59 tested, and thereafter it slowly declined. In all, 25 patients in the series developed such values at some time in the first eight weeks.

### *Serum Alkaline Phosphatase*

Elevated serum alkaline phosphatase levels tended to occur earlier than positive flocculation, but the proportion of the series showing such values was less. Altogether 26 patients (36%) showed values of 14 K.-A. units or more at some stage during the period. Of these, 12 had levels greater than 20 units, and five levels greater than 30 units. The highest level recorded was 67 K.-A. units.

Several other features regarding this investigation should be noted. Firstly, in 10 cases elevation of the serum alkaline phosphatase level occurred before any other biochemical evidence of liver involvement. Secondly, only three of the 26 patients were jaundiced, and the one with the highest level had no jaundice at any stage. Lastly, six patients had elevated levels in the sixth to eighth week, two of these having shown rising values over the whole period. Liver biopsy on one of these latter two patients at that stage revealed a focal lesion still present.

### *Bromsulphalein Retention*

Increased retention of bromsulphalein was common when the estimation was made during the fever, ranging from 1% to 35% in 30 patients so tested. Three patients retained less than 5% and three greater than 31%. The mean retention for the group was 16%.

When retention was estimated after the cessation of fever, the incidence of abnormal

retention was considerably less. In 50 patients so tested, the mean value was 5·5%, with a range from nil to 25%. Five patients retained nil and five retained 14% or more. Altogether, 17 of this group (34%) retained more than 5% of the administered dose.

TABLE I

| Period | Range (Units) | Mean (Units) | Number of Patients |
|---|---|---|---|
| 3rd to 6th day .. | 22–65 | 37·5 | 10 |
| 7th to 10th day .. | 15–170 | 44·0 | 26 |
| 11th to 14th day .. | 18–133 | 53·5 | 11 |
| 15th to 21st day .. | 10–106 | 34·2 | 8 |

### *Serum Transaminase*

Values for serum glutamic oxalacetic transaminase varied widely, but were at most only moderately elevated, the highest level recorded being 170 units. The test was performed 39 times on 31 patients during the first three weeks of the illness, with the results shown in Table I.

### *Combinations of Liver Function Tests*

With regard to the flocculation tests and serum alkaline phosphatase levels, the position may be summarized as follows:

| | |
|---|---|
| Abnormal results: | |
| All three tests .. .. .. | 10 patients |
| Cephalin-cholesterol flocculation and serum alkaline phosphatase tests.. | 10 patients |
| Cephalin-cholesterol flocculation test only .. .. .. .. .. | 21 patients |
| Serum alkaline phosphatase test only | 5 patients |
| Cephalin-cholesterol flocculation and thymol turbidity tests only .. | 14 patients |
| Serum alkaline phosphatase and thymol turbidity tests only .. | 1 patient |
| Thymol turbidity test only .. | Nil |
| Negative results in all three tests .. | 11 patients |
| Total .. .. .. .. | 72 patients |

TABLE II

*Details of Patients Submitted to Liver Biopsy, Showing Significant Results of Liver Function Tests Carried Out on the Days Nearest to the Day of Biopsy*

| Case Number | Duration of Fever | Day of Biopsy | Histology | Remarks |
|---|---|---|---|---|
| 44 | 7 | 6 | Normal, apart from small foci of mixed polymorphonuclear and round cells | 5th day: results of liver function tests normal |
| 53 | 14 | 9 | Some fatty change; some of lesions more sharply defined with central necrosis; marked portal-tract inflammation. (Figure I) | 7th day: results of liver function tests normal |
| 48 | 10 | 9 | Similar to Case 53. One granuloma in which inflammation is less intense and fibrosis is occurring. (Figure II) | 7th day: S.A.P.,[1] 19 K.-A. units; 12th day: S.A.P., 39 K.-A. units. |
| G.H. (i) | 19 | 9 | Slight fatty change; marked portal-tract inflammation; occasional degenerating liver cells scattered throughout; numerous focal necrotic areas with predominantly round-cell infiltration. (Figures III and IV) | 9th day: serum bilirubin content, 12·6 mg. per 100 ml.; C.C.F.T., +++; S.A.P., 14·2 K.-A. units; S.G.O.T.,[1] 50 units |
| G.H. (ii) | 19 | 22 | Similar to previous specimen, except foci are less numerous | 15th day: serum bilirubin content, 2·3 mg. per 100 ml.; C.C.F.T., ++++; T.T.T.,[1] 7 units; S.A.P., 21·1 K.-A. units; S.G.O.T., 40 units |
| 52 | 11 | 10 | Similar to Case 48 | Primary fever, 10 days; secondary fever, 13th to 19th days<br>9th day: results of liver function tests normal |
| 50 | 11 | 11 | Specimen fragmentary. One circumscribed lesion with central necrosis, but no fibrosis. A few other small foci present | 8th day: S.G.O.T., 50 units |
| 45 | 12 | 12 | Intense portal tract inflammation; an occasional small inflammatory focus; mild, diffuse polymorphonuclear infiltration | 9th day: results of liver function tests normal |
| 51 | 16 | 13 | Moderate fatty change; a few small inflammatory foci with marked portal-tract infiltration | 13th day: C.C.F.T., ++++; S.G.O.T., 47 units; B.S.P.,[1] 31%<br>Primary fever, 11 days; secondary fever, 13th to 16th day |
| 65 | 14 | 13 | Moderate bile-staining; isolated degenerating hepatic cells throughout; a few small inflammatory foci | 13th day: serum bilirubin content, 7·3 mg. per 100 ml.; C.C.F.T., ++; S.A.P., 39 K.-A. units; S.G.O.T., 48 units |
| 22 | 9 | 13 | Numerous foci, not well-demarcated; isolated degenerating hepatic cells; mild diffuse polymorphonuclear infiltration; portal-tract inflammation | 12th day: C.C.F.T., +++; S.A.P., 67 K.-A. units; S.G.O.T., 133 units |
| 21 | 24 | 15 | Moderate fatty change; focal inflammatory exudates as in earlier specimens; portal-tract infiltration is marked | 13th day: C.C.F.T., ++++; S.G.O.T., 133 units |
| 7 | 18 | 15 | Section appears identical with Case 21 | 13th day: C.C.F.T., ++++; S.A.P., 42·7 K.-A. units; S.G.O.T., 66 units; B.S.P., 23%<br>Primary fever, 9 days; secondary fever, 15th to 18th day |
| 1 | 18 | 55 | Normal, except for small foci, chiefly of round cells; portal tracts normal; no evidence of fibrosis | 40th day: C.C.F.T., ++++<br>Primary fever, 14 days; secondary fever, 17th to 18th day |
| 66 | 9 | 123 | Normal, apart from small focus of disintegrated hepatic cells with round-cell infiltration. | 52nd day: S.A.P., 29 K.-A. units; 16 weeks: S.A.P., 23 K.-A. units |

[1] S.A.P., serum alkaline phosphatase level; C.C.F.T., cephalin-cholesterol flocculation test; S.G.O.T., serum glutamic oxalacetic transaminase level; B.S.P., bromsulphalein retention.

*Morphological Observations*

Liver biopsy was performed upon 13 patients of the series at varying stages of the illness. There was no morbidity from the procedure. Biopsy was performed on only one of the three jaundiced patients, but serial biopsies have been performed on an additional jaundiced patient admitted to hospital subsequent to the closure of the series. Details of patients submitted to biopsy are given in Table II.

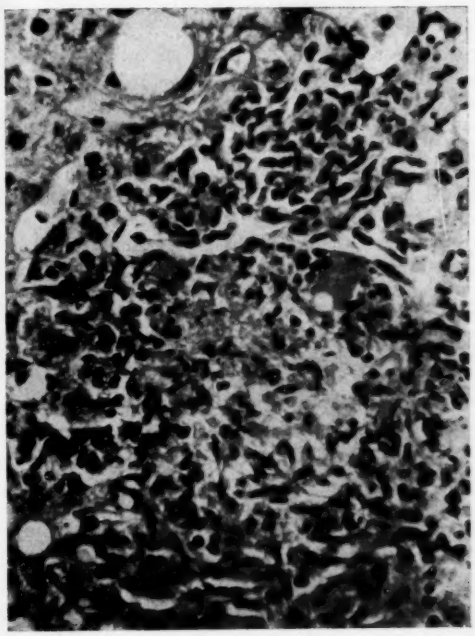

FIGURE I

Case 53. Typical inflammatory focus with necrosis and mixed-cell infiltrate. (Hæmatoxylin and eosin stain, high power)

There is, in all sections taken during the acute illness, a uniform pattern of focal inflammation. The degree and extent of this vary considerably, and there is some variation in the nature of the inflammatory exudate. In the earliest specimen (Case 44) there are a number of small foci scattered throughout normal parenchyma, and consisting of mixed polymorphonuclear and round cells. In sections taken several days later, there are seen, as well as these small, poorly-demarcated foci, sharply-defined collections of inflammatory cells with areas of frank necrosis in the centres of the lesions (Figure I). The exudate is composed of polymorphs, round cells, histiocytes and cells with elongated nuclei which are possibly Kupffer cells. In one section (Case 48) a definite granuloma with less intense inflammatory reaction, but with early fibrosis, is seen (Figure II). At this stage also there is found an intense portal and periportal infiltration with polymorphs, round cells and macrophages. In two specimens taken towards the end of the second week (Cases 22 and 65) there is in addition a more diffuse reaction. Isolated degenerating hepatic cells with dense clear-cut nuclei and disorganized cytoplasm are scattered at random throughout the section. In Case 22, in particular, the foci are much less well demarcated than in other specimens, and nothing approaching granuloma formation can be seen.

The histological picture in the section from G.H., taken at the height of jaundice, differs

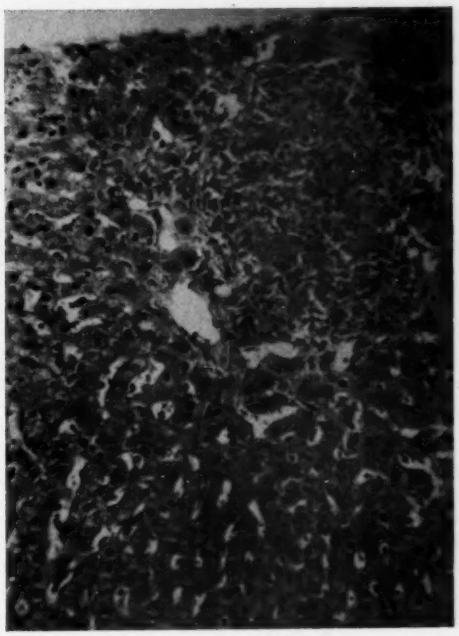

FIGURE II

Case 48. Isolated granuloma with central necrosis, somewhat less inflammatory reaction than in the previous section, and early fibrosis. The surrounding liver cells appear normal. (Hæmatoxylin and eosin stain, low power)

little from that already described. The focal collections are less well demarcated than in some other specimens, and mononuclears appear to be more prominent in the inflammatory exudate (Figures III and IV). In sections stained with Masson's trichrome stain quite

definite fibrosis can be seen in the foci, which also contain necrotic débris. As in one or two of the other specimens, occasional degenerating liver cells appear throughout the section. There is a moderate amount of bile-staining. In the biopsy from this patient taken on the

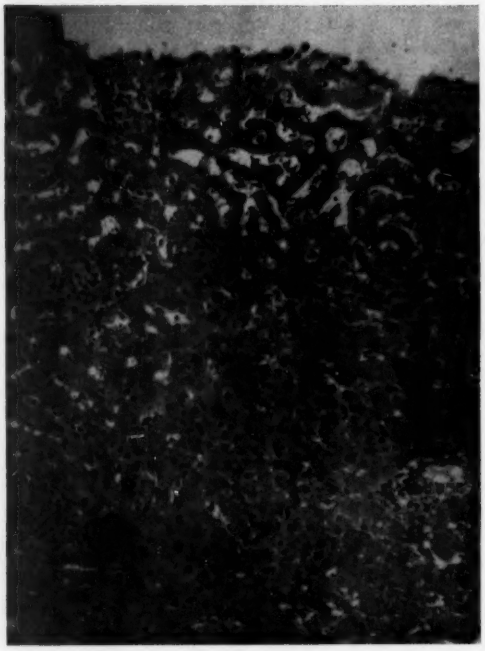

FIGURE III

G.H. Section from biopsy taken at the height of jaundice, showing scattered inflammatory foci amongst liver parenchyma, which is otherwise reasonably normal. (Hæmatoxylin and eosin stain, low power)

twenty-second day, the focal collections, whilst less numerous, differ not at all from those found 12 days earlier. The remainder of the liver parenchyma is normal.

In the material from Case 1, taken on the fifty-fifth day, the parenchyma appears normal, but there remains a number of small cellular collections, in which round cells are predominant, although polymorphs are also seen. There is no evidence of fibrosis, and the portal tracts are normal. Another patient (Case 66) was submitted to biopsy on the one hundred and twenty-third day, because of persistent malaise in association with a continuing elevation of serum alkaline phosphatase. For the most part the section shows normal liver parenchyma and normal portal tracts. However, in one area there is a small focus consisting of disintegrated hepatic cells with a moderate round cell infiltration.

## DISCUSSION

It is evident that abnormal results in various liver function tests, and particularly cephalin-cholesterol flocculation, are very common in "Q" fever, as seen in Brisbane. It is, of course, possible that increased flocculation is not in this instance evidence of hepatic disease, but rather may be a manifestation of some other factor, such as reticulo-endothelial response to infection. In this regard the relationship of this test to serum alkaline phosphatase levels is of interest, as elevated levels presumably reflect hepatic disorder in this condition. In Figure V are plotted the mean alkaline phosphatase values for groups of patients showing varying degrees of flocculation at different periods. It can

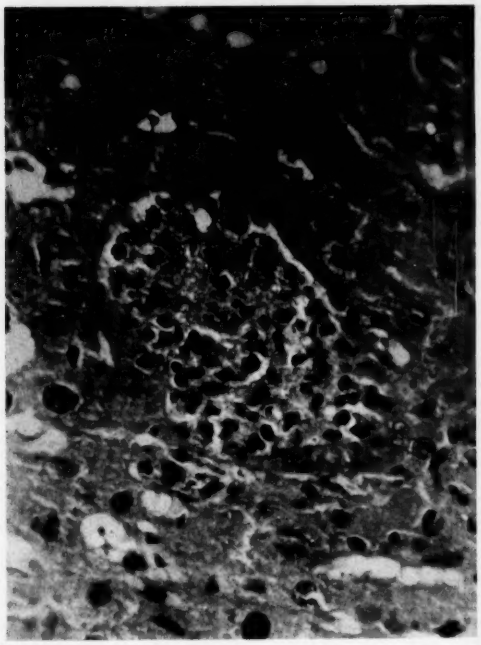

FIGURE IV

G.H. High-power view of focus present in Figure III. (Hæmatoxylin and eosin stain)

be seen that, excluding the earliest period, the mean values of the "+++"/"++++" groups are consistently higher than those of the "++" and "o"/"+" groups. It seems reasonable to assume, therefore, that cephalin-cholesterol flocculation and serum alkaline

phosphatase levels are related, and that the former can be regarded as valid evidence of hepatic involvement.

Thus, on the basis of routine liver function tests, it appears that liver involvement is very common in "Q" fever. In fact, as one of the biopsies which showed minor changes was performed on a patient who at no stage showed any abnormality in liver function tests (Case 45), it may be that a degree of liver involvement

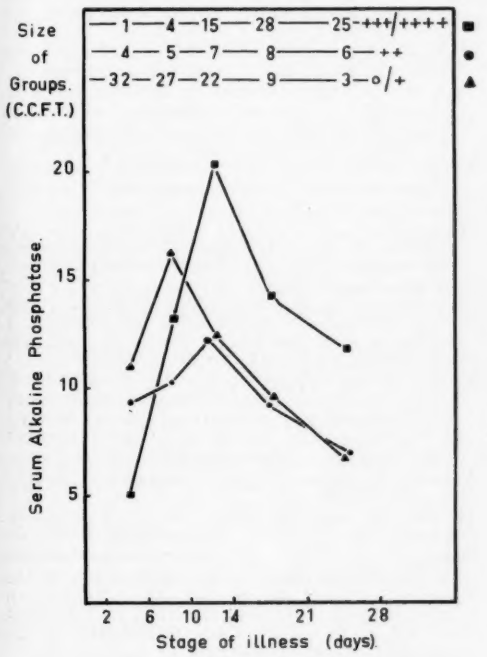


FIGURE V

Graph showing the mean serum alkaline phosphatase levels in groups of patients showing different degrees of cephalin-cholesterol flocculation at varying stages of the illness

is almost universal in the condition. This, of course, is no more than is to be expected in a condition which is undoubtedly a generalized disorder.

The serum alkaline phosphatase levels are of particular interest. The features which stand out are the occurrence of quite elevated levels in the absence of jaundice, the fact that at times a raised value may be the only evidence of hepatic involvement, and the high levels which occasionally occur. There seem to be two possible explanations for these features. First, if serum alkaline phosphatase elevation represents an obstructive factor in hepato-biliary disease, it may be that obstruction is important in "Q" fever hepatitis. Alternatively, it may be related to the type of lesion in the liver, as such a finding can occur in other granulomatous conditions (Popper and Schaffner, 1957). So far as the first alternative is concerned, it is possible that portal tract inflammation could provide the obstructive factor, although the biopsy material, which shows little evidence of bile stasis, hardly supports this theory. Nevertheless, it is difficult to see how jaundice of severe degree could occur in livers which show so remarkably little diffuse hepatocellular change unless some factor such as obstruction was playing a contributory part. In view of the essential similarity of all biopsy material, it is very unlikely that we are dealing with a process which is unevenly distributed throughout the liver, which is a further alternative.

This absence of widespread hepatocellular damage is reflected in the serum transaminase levels, which on the whole are not particularly high. In the one jaundiced patient in the series for whom these figures are available (Case 65), the S.G.O.T. on the sixth day was 65 units, the serum bilirubin content being 0·6 mg. per 100 ml. By the eleventh day, when the serum bilirubin level had risen to 5·5 mg. per 100 ml., the S.G.O.T. had fallen to 38 units. That this is no isolated phenomenon is shown by two other jaundiced patients who have been investigated subsequently. The first was admitted to hospital with a serum bilirubin content of 1·1 mg. per 100 ml., a bromsulphalein retention of 53%, and a S.G.O.T. level of 65 units. He became jaundiced two days later. Four days after that, the S.G.O.T. was 39 units. The second patient (G.H.), whose biopsy specimen has been described earlier, had a S.G.O.T. level of 50 units when the serum bilirubin content was 12·6 mg. per 100 ml. These low transaminase values accord fairly well with the relatively minor degree of hepatocellular necrosis in the biopsy material.

So far as the morphological picture is concerned, the constant feature is that of focal inflammation and necrosis, which varies in degree from small collections of cells to frank granuloma formation, with a fairly consistent portal tract inflammation at least in the acute stage, and occasionally, in addition, a rather more diffuse inflammatory reaction. There is evidence that, in some cases, the focal lesion may persist for several months.

From a clinical point of view, the chief interest of this study lies in the realization that "Q" fever may be of importance in the differential diagnosis of infective hepatitis in

certain areas and occupations. It must be appreciated that clinically the two conditions are probably indistinguishable. In this hospital we have for some time been interested in the problem of "Q" fever hepatitis, and yet in none of the cases in which jaundice was present could we feel certain, on clinical grounds, that we were dealing with this disease. Moreover, in recent months at least two further patients have been discharged from hospital with the misdiagnosis of infective hepatitis, to be discovered later only because routine serological investigations had been performed. Diagnosis of "Q" fever is always uncertain on clinical grounds alone, and particularly so in the jaundiced patient, whose condition can closely mimic infective hepatitis. However, suspicion should be aroused in relation to any patient in an appropriate occupation in whom headache, photophobia, cough and perhaps frequent rigors are prominent. It is emphasized that complement-fixation tests should be done as early as possible, to obtain a negative or low titre, and that a diagnostic rise, whilst it usually occurs about three weeks from the onset, may be delayed at times for a further two or three weeks.

Obviously needle biopsy of the liver is not to be recommended as a routine diagnostic procedure, as in any case diagnosis has little bearing on the patient's management. However, there may be occasions when it could be useful. It would then enable a presumptive diagnosis to be made, and would certainly exclude viral hepatitis, as well as other conditions such as leptospirosis (not uncommon in the particular occupation concerned), toxic hepatitis due to chemicals, and acute intrahepatic cholestasis due to drugs.

## ACKNOWLEDGEMENTS

I am grateful to Dr. I. R. Mackay, of the Walter and Eliza Hall Institute of Medical Research, for arranging the early transaminase estimations, and for critical advice. I must also thank Dr. J. I. Tonge, of the Queensland Laboratory of Microbiology and Pathology, for his great interest and help in the investigation.

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# INNOCENCE AND THE STAPHYLOCOCCUS[1]

V. D. PLUECKHAHN[2] AND JOAN BANKS[3]
*From the Geelong and District Hospital, Geelong, Victoria*

SUMMARY

A bacteriological and clinical survey is described of infection due to *Staphylococcus aureus* in 8473 babies delivered over the period 1956 to 1959 in a 95 bed maternity hospital. The incidence of minor staphylococcal disease was 41% at the commencement of the survey, and was reduced to 7·9% with the institution of accepted means of control.

A " carrier rate " of 90% of infants by the third and fourth days of life was present in 1957, and remained at this level in 1959 despite the reduction in the incidence of staphylococcal disease.

" Rooming in " and its part in the control of staphylococcal disease in the new-born are discussed.

Despite the consistently high incidence of minor staphylococcal disease in the new-born, the resultant morbidity in the first six months of life was low (0·3%) and the mortality less than 0·1%.

The incidence of breast abscess in 7438 mothers was 1·3%.

Phage pattern 80/81 and the question of " virulence " are discussed.

It is stressed that much remains to be discovered with regard to the modes of transmission of the staphylococcus and the part played by factors other than those directly related to the organism.

The Staphylococcus aureus is the commonest cause of neonatal infection in maternity hospitals and it causes a great variety of lesions.

—J. L. HENDERSON, Edinburgh, 1943.

As with leaders of countries so also with micro-organisms, their popularity, importance and lethality vary from generation to generation. In like manner some maintain the limelight longer than others and undoubtedly the grand old man among the bacteria is the staphylococcus which maintains this position in spite of all the writing and talking in attempts to destroy it.

Our interest in the problem of the staphylococcus and the new-born child was aroused three and a half years ago by the apparently high incidence of skin lesions, conjunctivitis and other minor cases of staphylococcal disease occurring in a new maternity hospital, which appeared to be on the increase despite the modern facilities offered.

The hospital under survey is the maternity wing of the Geelong and District Hospital, Victoria. The four-storied building, completed in 1953, serves a rural industrial city of 95,000 inhabitants and approximately 60 medical practitioners. It is staffed and situated quite separately from the 438-bed general hospital, and has a well-equipped delivery suite and 95 beds consisting of single rooms, two-bed and four-bed wards and one eight-bed ward. There is a general nursery on each floor and one central premature nursery. The nurseries vary from 342 square feet to 432 square feet in area, and there is in addition a changing and food preparation room attached to each.

The hospital performs all the public and private midwifery in Geelong and the surrounding districts for a radius of 20 miles. This results in approximately 2400 deliveries per year, of which slightly less than 80% are among private patients. This paper deals with all babies in the first 10 days of life in hospital, and in a limited number of cases, up to four weeks after their discharge. The average period of stay in hospital for each baby was eight days.

## METHODS

### *Nursing Methods*

These have been described previously (Plueckhahn and Banks, 1958). Since October, 1958, the handling of the umbilical cord has been standardized; the method used is a daily painting of the umbilical cord with a solution of 1·25% (w/v) iodine in 90% alcohol, the cord being left undressed from 12 hours after birth.

### *Bacteriological Methods*

Swabs were cultured on horse-blood agar plates and in nutrient broth. If staphylococci were not grown on the original plate, the broth was subcultured. All staphylococci isolated

[1] Received on May 2, 1960.
[2] Director of Pathology.
[3] Bacteriologist.

were tested for coagulase reaction by the slide method with human plasma. Throughout the paper, the term "staphylococcus" or "*S. aureus*" means a coagulase-positive *Staphylococcus aureus*. All sensitivity tests were made with Evans "Sentest" discs. The large majority of the phage typing was carried out by Dr. Hildred Butler, of the Royal Women's Hospital, Melbourne.

### *Recording of Incidence of Staphylococcal Disease*

One of us or a registrar examined all babies daily for four weeks in October and November, 1956, and again in February and March, 1957. From April, 1957, all babies were examined daily by the respective floor sisters or a member of our staff for even the slightest evidence of clinical infection. A swab for culture was taken from any suspicious area, and this included such minor lesions as reddened umbilical stumps, slightly sticky eyes and rashes. If *S. aureus* was grown, the baby was recorded as having staphylococcal disease. We are aware of the fallacies of this system, and often the presence of the staphylococcus was probably incidental and not the cause; on the other hand, there is no method of selection, as often a minor "sticky eye" or rash yields a profuse growth of staphylococci, and the severely inflamed eye or severe pustular lesion may yield no pathogens on culture.

TABLE I

*Infection Rate in Babies Grouped in Three-Month Periods from April, 1957, to December, 1959*

| Time | Babies Born | Infected Babies |
|---|---|---|
| 1957: | | |
| April–June | 557 | 193 (34·7%) |
| July–September | 616 | 207 (33·6%) |
| October–December | 654 | 216 (33·0%) |
| 1958: | | |
| January–March | 609 | 156 (25·6%) |
| April–June | 508 | 87 (17·1%) |
| July–September | 591 | 83 (14·7%) |
| October–December | 615 | 49 (7·9%) |
| 1959: | | |
| January–March | 594 | 54 (9·1%) |
| April–June | 559 | 100 (17·9%) |
| July–September | 607 | 75 (12·4%) |
| October–December | 633 | 67 (10·6%) |
| Total | 6543 | 1287 (19·7%) |

### *"Carrier Rates"*

On two days in May and September, 1957, and again in May and October, 1959, swabs were taken from both eyes, the nose and the umbilicus of all normal babies aged up to 10 days old. Nasal and hand swabs were also taken from the staff and mothers. Swabs were taken from the nose and hands of 100 consecutive ambulant women attending the pathology department for tests other than bacteriological tests. None of these women were in-patients or out-patients of the hospital. Vaginal, rectal and nasal swabs were taken from 100 mothers on commencing labour.

## RESULTS

The results of the various aspects of the survey are shown in Tables I to IX.

TABLE II

*Infant "Carrier Rate", 1957*

| Age of Babies | Number of Babies having Swabs Taken | Number Yielding S. Aureus | Site of Swabs Yielding S. Aureus | | |
|---|---|---|---|---|---|
| | | | Eyes | Umbilicus | Nose |
| 1–12 hours | 3 | — | — | — | — |
| 12–24 hours | 3 | 1 | — | 1 | 1 |
| 2 days | 13 | 8 | 4 | 6 | 5 |
| 3 and 4 days | 22 | 19 | 11 | 17 | 12 |
| 5 and 6 days | 38 | 38 | 28 | 28 | 33 |
| 7, 8, 9 and 10 days | 36 | 33 | 22 | 25 | 26 |

TABLE III

*Infant "Carrier Rate", 1959*[1]

| Age of Babies | Number of Babies having Swabs Taken | Number Yielding S. Aureus | Site of Swabs Yielding S. Aureus | | |
|---|---|---|---|---|---|
| | | | Eyes | Umbilicus | Nose |
| Birth | 20 | 3 | 2 | 1 | 2 |
| 1–12 hours | 10 | 5 | — | 3 | 1 |
| 12–24 hours | 11 | 8 | 1 | 7 | 1 |
| 2 days | 25 | 22 | 9 | 16 | 4 |
| 3 and 4 days | 50 | 45 | 22 | 34 | 23 |
| 5 and 6 days | 50 | 47 | 28 | 32 | 26 |
| 7, 8, 9 and 10 days | 55 | 51 | 26 | 36 | 35 |
| 14 days | 18 | 15 | 10 | 12 | 14 |
| 21 days | 19 | 14 | 12 | 7 | 10 |
| 28 days | 18 | 13 | 13 | 8 | 11 |
| 35 days | 19 | 13 | 11 | 10 | 10 |

[1] All babies aged 10 days and under had swabs taken in hospital. All babies aged 14 days and over had swabs taken in their own homes.

### *Incidence of Staphylococcal Disease*

All babies born after April, 1957, were examined daily while in hospital for signs of staphylococcal disease. In October and November, 1956, and in February and March, 1957, some 380 babies were examined in like manner, and *S. aureus* was isolated from lesions occurring in 156 (41·0%) of these babies. The incidence of staphylococcal disease in all babies born between April, 1957, and December, 1959, is shown in Table I.

### *"Carrier Rates"*

The "carrier rates" in babies during the two day surveys of 1957 and 1959 are shown in Tables II and III respectively.

Surveys of the hand and nasal carriage of staphylococci in mothers and nursing staff were made in 1957 and 1959. The results are shown in Table IV, which compares the "carrier rates" with those of the 100 normal women examined in 1959. The relative percentage of staphylococci resistant to penicillin is also included in Table IV.

TABLE IV

*Comparison of Nasal and Hand "Carrier Rates" in Mothers, Nursing Staff and Normal Women*

| Subjects | Number | S. Aureus Isolated | | |
|---|---|---|---|---|
| | | From Nose | From Hand | Penicillin-Resistant |
| Mothers: | | | | |
| 1956–1957 .. .. | 118 | 53% | 12% | 69% |
| 1959 .. .. | 70 | 64% | 74% | 85% |
| Nursing staff: | | | | |
| 1956–1957 .. .. | 130 | 68% | 28% | 85% |
| 1959 .. .. | 70 | 74% | 47% | 84% |
| Normal women: | | | | |
| 1959 .. .. | 100 | 34% | 21% | 22% |

In 1959, vaginal swabs were taken from 100 consecutive mothers on commencing the final stages of labour. The results of these swabbings, together with those of nasal and rectal swabs taken at the same time, are shown in Table V.

TABLE V

*Nasal, Vaginal and Rectal "Carrier Rates" of Staphylococci in 100 Mothers in Labour*

| Site of Isolation of S. Aureus | Number of Cases |
|---|---|
| Nose .. .. .. .. | 52 |
| Vagina .. .. .. | 1 |
| Rectum .. .. .. .. | 4 |

### *Severe Staphylococcal Disease in Infants*

A very complete follow-up investigation of all babies born was possible, as the Geelong and District Hospital provides more than 90% of the public and private hospital beds available to the population of Geelong and its surrounding districts. There was, in addition, complete cooperation by all medical practitioners in the area in giving information concerning their private patients and completing a pro-forma circulated to them at three-monthly intervals. This was further supplemented and cross-checked by information derived from private and public hospital records and from coronial autopsies.

The number of infants requiring hospitalization or dying as a result of staphylococcal disease in the first six months of life is shown in Table VI.

TABLE VI

*Infants Developing Severe Staphylococcal Disease in First Six Months of Life*

| Period | Infants Born in the Hospital | Number Admitted to Hospital for Staphylococcal Disease | Deaths in First Six Months of Life |
|---|---|---|---|
| July to December, 1956 .. .. | 1298 | 6 | 1 |
| 1957 .. .. | 2419 | 11 | 4 |
| 1958 .. .. | 2323 | 7 | 2 |
| 1959 .. .. | 2433 | 7 | 1 |
| Total .. | 8473 | 31 | 8[1] |

[1] Due to following: pneumonia, 6 cases; septicæmia, 1 case; peritonitis, 1 case.

### *Breast Abscess in Mothers*

The incidence of breast abscess developing in mothers during the survey is shown in Table VII.

TABLE VII

*Incidence of Breast Abscess Developing in Mothers within Six Months of Delivery*

| Period | Number of Mothers | Number Breast Abscesses | Percentage of Mothers Developing Breast Abscesses |
|---|---|---|---|
| July to December, 1956 .. .. | 1091 | 27 | 2·5 |
| 1957 .. .. | 2003 | 31 | 1·5 |
| 1958 .. .. | 2024 | 20 | 1·0 |
| 1959 .. .. | 2320 | 18 | 0·8 |
| 1956–1959 .. | 7438 | 96 | 1·3 |

### *Phage Group Distribution of Staphylococci Isolated*

The term phage pattern 80/81 has been used for convenience to include the strains typing as 52/80/81, 52/52A/80/81, 80, 80/81 and 81, as all these have been found to be closely related (Asheshov and Rippon, 1959; Rountree, 1959).

The frequency of the various phage groups isolated in the maternity wing in 1957 and 1959 is shown in Table VIII.

Table IX compares the phage types of the staphylococci isolated from lesions in the maternity wing with those isolated from lesions in the wards of the general hospital.

TABLE VIII

*Distribution of Phage Groups in the Maternity Wing in 1957 and 1959*

| Phage Type | Babies: Minor Lesions | | Mothers: Hands and Nose | | Staff: Hands and Nose | | "Normal" Women |
|---|---|---|---|---|---|---|---|
| | 1957 | 1959 | 1957 | 1959 | 1957 | 1959 | 1959 |
| Group I: | | | | | | | |
| 80/81 .. | 5 | 12 | — | 4 | 12 | 14 | — |
| Others .. | 7 | 3 | 1 | 1 | 8 | 4 | — |
| Group II .. | 2 | 5 | — | 2 | 7 | 4 | 8 |
| Group III .. | 17 | 12 | 5 | 10 | 7 | 10 | 9 |
| Miscellaneous .. | 1 | 4 | — | 1 | 4 | — | — |
| Non-typable .. | 6 | 63 | 8 | 8 | 13 | 38 | 27 |
| Total .. | 38 | 99 | 14 | 26 | 51 | 70 | 44 |

## DISCUSSION

Intense interest in this problem over the past ten years had tended to give the impression that the position in relation to the staphylococcus and the new-born child has worsened in this decade. Is this so? There were 2917 deliveries at the maternity hospital concerned in our surveys between January 1, 1958, and March 31, 1959, and some 420 of these babies developed a staphylococcal lesion within the first ten days of life. Henderson (1943) reported 424 babies developing staphylococcal lesions at the Simpson Maternity Hospital, Edinburgh, in 1942, from slightly less than 2800 deliveries. These figures are not strictly comparable, but tend to show that the position has not materially worsened since then, and are in agreement with those of Walsh McDermott (1956), who wrote:

> We have no convincing evidence, or indeed any particularly well founded suspicion, that the crude equilibrium between the public at large and the ubiquitous staphylococcus is shifting for the worse.

TABLE IX

*Comparison of Phage Groups in the Maternity Wing and in the General Hospital*

| Phage Type | Maternity Wing | General Hospital | |
|---|---|---|---|
| | | All Ages | <Six Months Old |
| Group I: | | | |
| 80/81 .. .. | 17 | 37 | 11 |
| Others .. .. | 10 | 1 | — |
| Group II .. .. | 7 | 3 | — |
| Group III .. .. | 29 | 6 | 2 |
| Non-typable .. .. | 69 | 6 | 5 |
| Total .. | 137 | 56 | 18[1] |

[1] Also included in all ages.

Our early surveys (Plueckhahn and Banks, 1958) showed that the staphylococcus was exceedingly prevalent, and that the understanding of modes of infection and cross-infection by the nursing and medical staff was not good; this was particularly so in the nurseries, where the observance of even first principles was poor. Very significant was the busy life of the majority of babies, who at feeding times were handled by several people and generally weighed on scales which were used for "infected" and "clean" babies alike. If the skin of the babies escaped injury and the staphylococcus during these procedures, it was even more likely to become infected when they were undressed once a day and fully bathed in baths from 50% of which profuse growths of *S. aureus* could be grown. Between handlings, the baby slept in an attractively painted modern nursery, where the air was kept moving by the coming and going of nursing and medical staff, the washing and changing of other babies, the making of cribs and the sorting of dirty linen. The nursing staff washed hands between handling the babies in modern basins separated from the nurseries by doors, from the handles of which the staphylococcus could often be grown. Even if the door handles were not touched, the conscientious nurse going back and forth to wash her hands kept the doors swinging and the air moving.

The amount of movement by staff in a large maternity hospital with central nurseries for the babies and private rooms for mothers is amazing. A rough assessment of this was given by providing patients with automatic counters and requesting them to press the key every time a member of staff came into the room. Six mothers in single rooms each averaged 139 visits on the first day after delivery and 115 visits on the second day. These included bringing the baby in and out, food trays, bedpans, dressings, flowers and letters, and the other numerous interruptions complained of by "tired mothers".

We have previously described in detail the changes recommended as a result of these initial surveys (Plueckhahn and Banks, 1958). Much emphasis was laid on reeducation of the nursing and medical staff in the first principles of control of cross-infection and infectious disease. Hand-washing techniques and facilities

were altered, and marked limitations in handling the babies by staff were enforced. The time-honoured ritual of a daily bathing of the baby was stopped, and weighing of the infant considerably reduced. As far as the umbilicus and eyes were concerned, an attempt was made to standardize or to eliminate the many and frequent forms of abuse to these areas by various antiseptic and antibiotic solutions, which often were applied four-hourly in concentrated forms to normal tender conjunctiva for no reason other than a " weeping " eye.

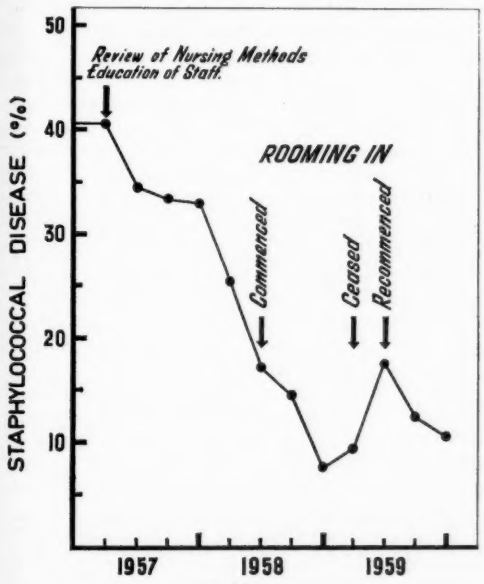


FIGURE I

The curve shows the incidence, in three-monthly periods, of staphylococcal disease in babies. The sharp drop in the incidence following a review of nursing methods and education of staff in March, 1957, is clearly shown. The curve also shows the effect of commencing and ceasing " rooming in " in 1958 and 1959

With the observation of first principles and education of the staff, the severity of lesions noticeably decreased and the reported cases of even minor staphylococcal disease slowly fell (Figure I).

Special " rooming in " cots were purchased in July, 1958, and after this the babies were removed from the central nurseries after the first 24 hours of life and cared for by their mothers. The only exceptions were for medical reasons, in approximately 5% of cases. This was followed by a further drop in the number of cases, and the improvement was maintained until April, 1959, when the incidence of minor staphylococcal disease rose rapidly (Figure I). This rise was interesting, as at the end of March, 1959, the staff was instructed to move the babies and cots back to the nurseries during visiting periods and at night—in other words, the beginning of the breakdown of " rooming in ". This was precipitated by lay complaints to hospital committee members that some babies were being handled by visitors. Full " rooming in " was reinstituted again in July, 1959 (Figure I), and was followed by a slow drop in the incidence of staphylococcal disease.

### *Staphylococcal Infection of Eyes*

Experience during the survey has shown that routine eye toilets serve no useful purpose in preventing " sticky eyes ", but may amount to unnecessary and dangerous interference by increasing the risk of cross-infection and the possibility of minor trauma to the conjunctiva and eyelids. Damage to an epithelial surface provides not only a portal of entry, but also an area for localization and multiplication of any staphylococci lodging there.

A comparison of the incidence of staphylococcal disease of the eyes on the individual floors of the maternity wing during the surveys in October and November, 1956, and again in March and April, 1957, is shown in Table X.

TABLE X

*Comparison of Staphylococcal Disease of the Eyes on Individual Floors of the Maternity Hospital*

| Floor | Infants at Risk | Sticky Eyes |
|---|---|---|
| Ground .. | 85 | 12·4% |
| First .. .. | 71 | 12·7% |
| Second .. | 83 | 13·2% |
| Third .. .. | 71 | 4·9% |
| Total .. | 310 | 10·7% |

These results show that the third floor had the lowest incidence of " sticky eyes ", and this floor was in charge of an overpowering but extremely competent and dogmatic elderly sister, who believed in leaving the eyes absolutely alone unless " definitely infected ". On all other floors routine eye toilets were carried out whether the eyes were " sticky " or not. These findings added weight to a policy of stopping routine procedures on the baby which appeared to have no scientific basis. The prophylactic instillation of antibacterial drops and ointments in the eyes and routine eye toilets were considered in this group, and were

stopped among public patients early in 1957. This was almost universally accepted and adhered to by the general practitioners among their private patients. The steady fall in the incidence of " sticky eyes " is shown in Table XI.

TABLE XI

*Incidence of " Sticky Eyes " due to Staphylococcal Infection, 1956–1959*

| Year | Staphylococcal Eye Disease | |
|---|---|---|
| | Infants at Risk | Percentage Infected |
| 1956 (three months) .. | 1298 | 12·4% |
| 1957 .. | 2419 | 9·9% |
| 1958 .. | 2323 | 6·8% |
| 1959 .. | 2433 | 5·8% |

There was no case of gonococcal ophthalmia during this period. We consider that no form of eye toilet is justified—not even the much-beloved one " quick wipe " with a moist " clean " swab at birth, which procedure is extremely difficult to stop, especially among the older general practitioners and nursing sisters. We have grown *S. aureus* in abundant growths from the eyes of two babies less than one hour old (Table III). These organisms must have been introduced either by the " quick wipe " at birth or from the mother's vagina.

TABLE XII

*Cultures of Vaginal Swabs in 1958 and 1959*

| Source | Swabs Taken | No Growth | S. Aureus Grown | Moniiia Albicans | Bacterium Coli and Other Organisms |
|---|---|---|---|---|---|
| Ante-natal | 125 | 55 | 3 | 40 | 17 |
| Puerperal | 61 | 27 | 1 | 1 | 32 |
| Incomplete abortion | 100 | 51 | 7 | 3 | 39 |

### *Vaginal Staphylococci*

The data in Tables V and XII suggest that vaginal contamination plays a minor part in neonatal staphylococcal infection. Table XII is compiled from all vaginal swabs taken in the maternity wing and the ante-natal clinic during the years 1958 and 1959 from any patient showing vaginitis, abnormal discharge or offensive lochia. Also included are vaginal swabs taken from patients whilst in hospital after an incomplete abortion in the early months of pregnancy.

These results are in agreement with those of Wysham *et alii* (1957), who grew no coagulase-positive staphylococci from vaginal cultures taken from 99 mothers just after delivery, and are contrary to the findings of Bret *et alii* (1959), who found that at the time of confinement 15% of 300 consecutive mothers were carriers of pathogenic staphylococci in the vagina. The latter authors were also of the opinion that in 82% of these women the fœtus was infected during labour (12·5% of confinements). We cannot agree with their opinion that searching for and treating vaginitis in pregnant women would play much part in the prophylaxis of staphylococcal disease in the new-born infant.

In July, 1959, a surprise " spot check " of the " sterile delivery trolleys " in the eight labour wards showed how ubiquitous the staphylococcus is. These trolleys are made up after each delivery, and periods from one hour to two days may elapse before their next use. It was a routine procedure to include a small stainless steel bowl containing " sterile " water and swabs on these trolleys, and these were used if required for the " quick wipe " of eyes at birth. A swab taken from one stainless steel bowl resulted in a growth of five colonies of *S. aureus*.

### *" Carrier Rate " of S. aureus*

The " carrier rate " of *S. aureus* remained virtually unchanged over three years, despite the care taken to prevent cross-infection and a marked reduction in both the severity and incidence of clinical staphylococcal disease (Figure II).

This figure shows that by the third and fourth days, 90% of the babies carried the staphylococcus. Appreciation of the high " carrier rate " in new-born babies is not recent, as Benians (1943) reported a " carrier rate " of almost 100% of all babies 10 days old.

A point of interest in Table IV is the great increase in 1959 in hand " carrier rate " of the mothers consequent to handling their own babies after the adoption of " rooming in ".

### *Staphylococcal Disease in First Six Months of Life*

All babies born were closely followed for six months after leaving hospital, and very few were readmitted as a result of staphylococcal disease in this period (Table VI). Fewer still died from staphylococcal disease (Table VI). These figures are complete, and include cases of sudden death coming under the jurisdiction of the coroner.

Approximately 90% of the mothers were followed for six months after their discharge home, in order to determine the incidence of

breast abscess (Table VII). The figures include only those breast abscesses which either required treatment in hospital, or discharged and were treated at home. Breast infections which completely resolved under chemotherapy were not included.

Although the maternity hospital under discussion has an apparently higher than usual incidence of staphylococcal disease in the new-born, the morbidity to babies (Table VI) and mothers (Table VII) is as low as or lower than other recorded surveys (Webb, 1954; Ravenholt *et alii*, 1957; Knight and Nolan, 1959). The last-mentioned authors estimated, from a review of hospital records in Edinburgh in 1957, that between 3% and 4% of all women delivered developed breast abscesses requiring hospital treatment.

### *Phage Patterns and Disease*

Four hundred and ten strains of *S. aureus* were phage-typed (Tables VIII and IX). Phage pattern 80/81 was prominent, as in reports from other maternity hospitals in Australia and elsewhere in the world (Rountree and Freeman, 1955; Gillespie and Alder, 1957; Monro and Markham, 1958; Timbury *et alii*, 1958). At no time has any particular pattern assumed epidemic proportions. Timbury *et alii* (1958) reported that the introduction of type 80 to the Royal Maternity Hospital, Glasgow, was closely followed by a sudden and dramatic increase in the severity of infections among the babies. They, like many previous workers, regarded the strain as unusually virulent, and were also of the opinion that it did not have great powers of colonization. Our figures are small, but tend to show that staphylococci of phage pattern 80/81 were not responsible for any increased incidence, severity or clinical type of lesion amongst the babies; in fact, the proportion of staphylococci of phage pattern 80/81 isolated from lesions of the new-born has remained almost constant over the entire survey (Table VIII).

Various writers (Barber and Burston, 1955; Gillespie *et alii*, 1958; Williams, 1959) consider that Group I strains are much more frequent in maternity hospital outbreaks than in surgical ward outbreaks. We have found the reverse in our limited experience, and there has been a marked predominance both in 1957 and in 1959 of phage pattern 80/81 in the staphylococcal lesions seen in the general hospital (Table IX).

Initially we were disturbed by the large number of non-typable staphylococci isolated from lesions in the maternity wing in 1959. Dr. Hildred Butler of the Royal Women's Hospital, Melbourne, confirmed that they were in fact non-typable. Whether these are a new type or of some other significance is still under investigation.

Many questions need to be answered before staphylococci of phage pattern 80/81 are considered distinct from other members of Group I, or for that matter, from staphylococci generally. Little is really known of virulence and immunity in relation to the staphylococcus.

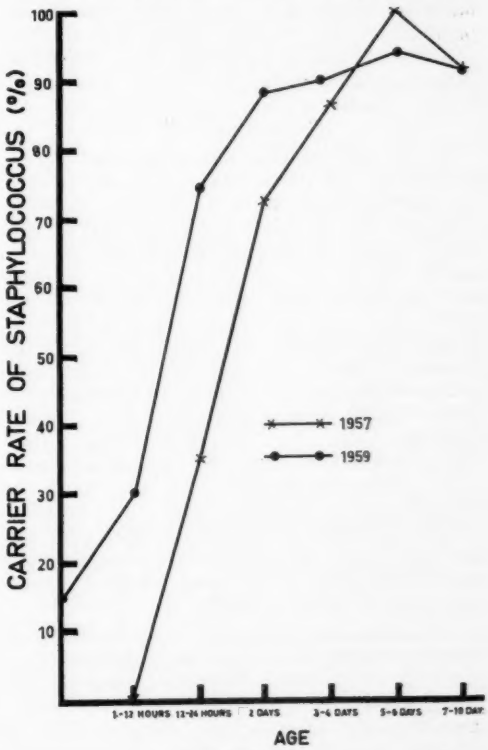


FIGURE II

This figure is derived from data in Tables II and III, and compares the infant "carrier rates" in the surveys of 1957 and 1959

Neither property is absolute, and many factors not related directly to the organism itself affect the result of the host-parasite relationship. Human experiment by Elek (1956) and Elek and Conen (1957) showed no gross difference in virulence to human beings between the various coagulase-positive strains of *S. aureus*. The main pattern of infection by the staphylococcus is localization and infiltration rather than colonization, and any breach in an epithelial surface with a few hours' unrestricted growth forms an excellent beachhead from which it may

be hard to dislodge the organism; once this has happened, the result probably depends more on the host than on the parasite.

There is no fundamental difference between staphylococcal disease in the new-born and wound infection in a surgical ward; an injured epithelial surface is the initiating factor. What does differ is the method by which the staphylococcus arrives in this breach; in surgical wounds this probably is preventible, in the baby it is probably not. What should be preventible in the latter is the initial production of a minor wound by indecencies to the epithelial surfaces of the baby.

### *" Rooming In "*

In the past decade, much has been written on methods of control of the staphylococcus in maternity hospitals, and lately emphasis has been placed on chemical means. That the latter is not the ultimate answer was pointed out by Kossiakoff in the first volume of *Annales de l'Institut Pasteur* (1887), in an article on " The Properties which Microbes Possess to Adapt Themselves to Antiseptic Environments ". Are our thoughts being concentrated in the right direction? Little is really known of the habits and the transmission of the staphylococcus, other than in quite general terms. That the hospital, its staff and environment play a big part in the transmission of the staphylococcus is known, and this must be greatly increased with the modern trend of building larger and multistoried buildings with central facilities which throw mothers, babies and staff in close proximity.

Whatever the habits of the staphylococcus, there are four main links in the chain of staphylococcal disease in the new-born; these are the maternity hospital itself, its staff, the mother and the baby (Figure III). All must play a greater or lesser part in cross contamination. Our results suggest that properly conducted " rooming in " is an essential step in combating the problem in a large hospital (Figure I). It is clear that, if the mother and infant are cared for as a single unit, many avenues of cross-infection will be eliminated (Figure III). With " rooming in " it becomes even more incumbent on the nursing staff to observe strictly the first principles of aseptic technique whenever they intrude in this family unit.

Unfortunately, the enforcement of strict " rooming in " does suffer certain opposition from both the mothers and the nursing staff. Many of the former, particularly those with a family, regard their respite in hospital as a holiday, or at least as an escape from the cares of running a household and the cries of older children. On the other hand, the obstetric nurse is often attracted to that career by a love of handling new-born babies, and once this is limited or removed, much of her interest in maternity nursing goes. There is thus an ever-present need for sympathetic and constant education to both these groups to overcome this problem.

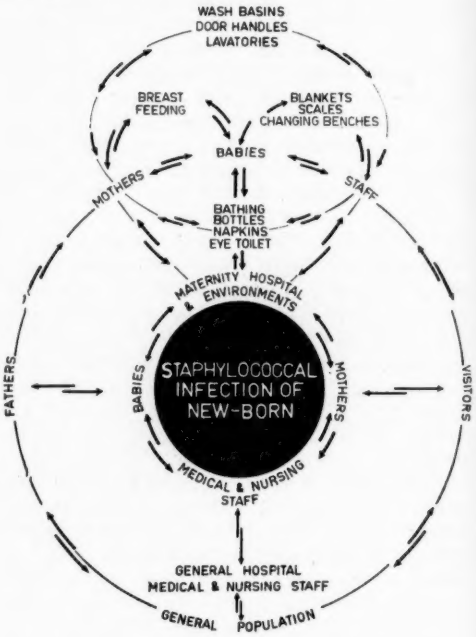


FIGURE III
Modes of transmission of the staphylococcus

### *Antibiotic and Antibacterial Substances*

Many hospitals have tackled the problem of the staphylococcus and the new-born child by concentrating on lowering the nasal " carrier rate " in staff and babies, and results have often been heartening. There is undoubtedly justification for the use of antibiotic cream in the nose when combating temporary outbreaks of severer and more prevalent staphylococcal disease; but whether the constant use of these substances is advisable is an entirely different question (Rountree and Barbour, 1951; Monro and Markham, 1958). It is possible, particularly in the baby, that the removal of one organism may well make the way clear for colonization of the nose by another more troublesome organism. Other workers have concentrated more on the baby itself, and have investigated the application of substances such

as hexachlorophene and chlorhexidine to the skin of the baby in attempts to kill any staphylococcus lodging there (Hardyment, 1954; Gillespie *et alii*, 1958; Simpson *et alii*, 1960).

These methods have yielded very encouraging and often spectacular results. Hill *et alii* (1959), by the application of hexachlorophene emulsion to the skins of babies, report a reduction in staphylococcal disease in six months from 15% to 1·3% of the babies born at the Royal Women's Hospital, Melbourne.

These measures keep the problem constantly before all people handling the babies, and result in better observation of first principles which may well prove to be the more important factor. At best, control by antisepsis is but a part answer to the eradication of any infectious disease—the staphylococcus cannot be the exception.

Finally, " in spite of the vast efforts to probe into the pathogenesis of staphylococcal infections we are still ignorant of many of the basic facts " (Elek, 1959), and innocence does not apply only to the new-born.

## ACKNOWLEDGEMENTS

We thank the Acting Medical Superintendent of the Geelong and District Hospital for permission to publish this paper. We also thank all medical practitioners in the area, the nursing staff and the hospital committee for their full cooperation in this survey. We acknowledge our indebtedness to Dr. Hildred Butler for much of the phage-typing.

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*A Review Written by Request*

# THE DROWNED LUNG

## A PHYSIOLOGICAL APPROACH TO ITS MECHANISM AND MANAGEMENT[1]

D. F. J. HALMAGYI[2] AND H. J. H. COLEBATCH[3]
*From the Department of Medicine, University of Sydney*

> It is in the mouth of everybody that a little brandy will kill a cat. I have made the experiment. In all those cases where it kills the cat it does so by getting into her lung and not her stomach.
>
> —JOHN HUNTER (1781).

THE picturesque term "drowned lung" was first used more than half a century ago by Chevalier Jackson (Jackson and Jackson, 1950) to describe a condition characterized by the penetration of fluid into the air passages. He suggested that the fluid causes airway obstruction and should be removed by suction. This treatment proved to be dramatically successful in many cases; however, it failed completely in others (Hatch and Carrera, 1959).

### CAUSES OF FLUID IN AIR PASSAGES

Penetration of fluid into the airways is a common occurrence in numerous conditions (Table I). Aspiration of amniotic fluid has been blamed as a major cause of perinatal mortality (Barnett, 1959). Inhalation of milk and feeding mixtures in the very young (Moran, 1953) and the very old (Gardner, 1958) appears to be more frequent than is generally recognized. The significance of drowning or near-drowning does not need special emphasis (Donald, 1955; Bowden, 1957; Hickey, 1959).

In another group of maladies, fluid in the airways is a consequence of an increased rate and volume of secretions. Different terms are used in the literature to describe this condition—"autodrownage" (Jackson and Jackson, 1950), "secretional ventilatory obstruction" (Nelson, 1958), and "*bronchoplégie œdémateuse*" (Brun *et alii*, 1960), to mention only some of the more recent ones. The most common members of this group are bronchitis and lung œdema. In bronchitis and status asthmaticus, thick tenacious secretions occlude the lumina of the airways. In "bronchiolitis" of children (Martin and Morgon, 1959) and in the so-called "Asian influenza" (Barrowcliff and Prior, 1957), in which the bronchitis is fulminant and the amount of secretions is excessive, there results a characteristic and often fatal clinical syndrome resembling drowning. In acute lung œdema, fluid enters the alveoli from the capillaries in an explosive way, fills them quickly and pours into the airways. In blast injury (Williams, 1942–1943; Zuckerman, 1940–1941) and in rapid decompression (Fegler and Banister, 1944–1946) the airways are filled up rapidly with blood originating from the ruptured capillaries and alveoli. In severe chest trauma (Burford and Burbank, 1945; Brewer *et alii*, 1946; Harper and Tait, 1946) the increased fluid content of the lung is often regarded as the cause of death ("wet lung", Daniel and Cate, 1948). The origin of the fluid is not well understood; some regard it as increased bronchial secretions, others as œdema fluid.

Diseases affecting the mechanism of deglutition and coughing are well known to facilitate the collection of fluid in the airways; they will not be mentioned here in detail.

Unconsciousness and anæsthesia are the conditions in which penetration of fluid into the airways is most likely to occur. Inhalation of saliva and gastric content was fatal in 92 out of 1100 cases of general anæsthesia (Edwards *et alii*, 1956). Delayed gastric emptying during parturition appears to be responsible for the relative frequency with which aspiration of vomitus contributes to maternal death (Mendelson, 1946; Parker, 1954). Half the mortality rate in severe head injuries is said to be due to the inhalation of saliva, vomitus, blood and cerebro-spinal fluid (Maciver *et alii*, 1958). Post-operative pulmonary atelectasis (also called "congestive atelectasis" by Jenkins *et alii*

[1] Received on November 4, 1960.
[2] Adolph Basser Research Fellow of The Royal Australasian College of Physicians.
[3] Joint Coal Board Research Fellow.

TABLE I

*Classification of the Drowned Lung*

| Origin of Fluid | Source of Fluid | Nature of Fluid | Composition of Fluid | Clinical Condition |
|---|---|---|---|---|
| Aspirated | Endogenous | Saliva | Isotonic, low protein | Unconsciousness, Anæsthesia, Bulbar paralysis |
| | | Gastric content | Low protein, low pH | |
| | | Blood | Isotonic, high protein | |
| | | Cerebro-spinal fluid | Isotonic, low protein | Head injuries |
| | Exogenous | Fresh water | Hypotonic | Drowning |
| | | Sea water | Hypertonic | |
| | | Drinks, feeding mixtures | Often alcoholic or hypertonic | |
| | | Amniotic fluid | Isotonic, low protein | Newborn |
| Secreted | | Blood | Isotonic, high protein | Blast injury |
| | | Bronchial mucus | Isotonic, viscous, high protein | Bronchitis, toxic gases and vapours, foreign body aspiration, defective cough reflex |
| | | Alveolar transudate | Isotonic | Lung œdema |

(1950) and by Hatch and Carrera (1959)), was shown to be the consequence of fluid aspiration into the lungs (Leopold, 1924; Lee *et alii*, 1928; Palmer and Sellick, 1953). Drunken unconsciousness appears to involve special dangers; the inhalation of concentrated alcohol was shown to result in particularly severe histological changes in the lungs (Moran and Hellström, 1957).

## CLINICAL, HISTOLOGICAL AND RADIOLOGICAL FEATURES

The clinical signs and symptoms of these different forms of fluid aspiration are essentially similar, and consist of severe dyspnœa and cyanosis, accompanied by tachycardia and wheezing. Breathing of 100% oxygen is usually ineffective in relieving these changes (Hatch and Carrera, 1959), and the progression towards right heart failure appears to be largely unaffected by digitalis.

It appears logical to describe radiological and post-mortem changes simultaneously; they have been compared by numerous authors. No radiological or pathological alterations were detected in some cases (Werne and Garrow, 1953; Hickey, 1959; and others). In others, irregular mottled opacities with areas of confluence around the hilum were described (Williams, 1942–43; Fegler and Banister, 1944–46; Burford and Burbank, 1945; Mendelson, 1946; Brewer *et alii*, 1946; Trocmé *et alii*, 1947 and 1949; Daniel and Cate, 1948; Romagosa *et alii*, 1950; Saline and Baum, 1954; Reboul *et alii*, 1955). The X-ray appearance was often indistinguishable from that seen in lung œdema (Gould and Torrance, 1955). Histological findings in these cases consisted of large areas of collapse accompanied by fluid-filled alveoli and/or foam-filled airways (Mendelson, 1946; Teabeaut, 1952; Moran, 1953; Barrowcliff and Prior, 1957). The remarkable similarity of these ætiologically widely different maladies is demonstrated in Figures I to V.

## PATHOGENESIS OF ATELECTASIS

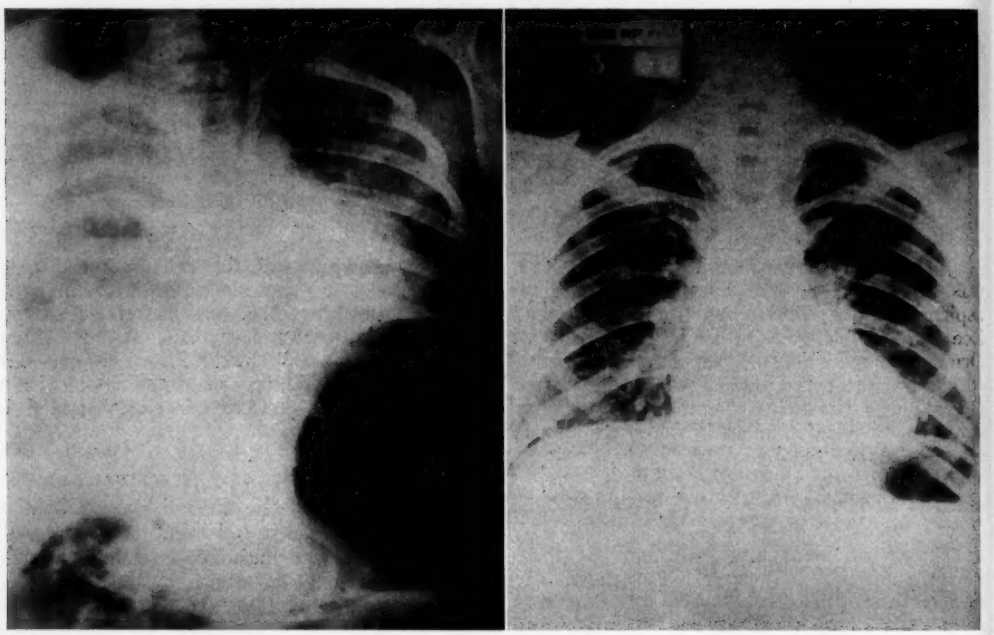
It appears that the most likely explanation of the X-ray opacities is that they represent atelectatic areas. Pathologists usually tend to differentiate an "absorptive" and a "congestive" form of atelectasis. In the former, some mechanical obstruction of the airways could be demonstrated and was considered as a sufficient explanation. In the latter, no obstruction could be detected and the relative prominence of the capillaries after the collapse of the alveoli led to this descriptive term. However, according to more recent data to be presented in this paper, the latter term is unjustified, and fails to contribute to our understanding of the process by which areas of the lung collapse in the absence of visible mechanical obstruction.

Provided the subject has been breathing air and not pure oxygen prior to obstruction of the airways, atelectasis will take several hours to develop. The delay is due to the gradual absorption of air as opposed to pure oxygen (Dale and Rahn, 1952). Radiological opacities following the inhalation of fluid were shown to develop within several minutes by some of the above-mentioned authors.

Fluid in the lungs is absorbed across the entire alveolar-capillary surface, the size of which is equal to a squash-court. This is why it takes only a few minutes for 80% of the inhaled water to disappear from the lungs (Courtice and Phipps, 1946; Courtice and Simmonds, 1949). Radiological opacities following the inhalation of fluid were shown by some of the above-mentioned authors occasionally to persist for several days.

about 35 mm. of mercury. Since this pressure cannot be produced continuously, the terminal airways or the alveoli so affected would close. This effect of water should be more or less independent of its volume, since a very thin layer of water would be effective immediately.

In cases in which fluid is secreted from the capillaries, as in lung œdema or blast injury, some of the alveoli will first be filled up. Then only will the fluid and the foam invade the



(*a*) (*b*)

FIGURE I

Near-drowning in sea water, boy, aged 12 years: (*a*) at admission; (*b*) 24 hours later, complete recovery. (By the courtesy of Sutherland Shire District Hospital)

Alveoli have the ability to remain expanded at the relatively low transpulmonary pressure produced during quiet breathing. In other words, the tendency of their curved surface to contract (surface tension) is counterbalanced by a rather low (5 mm. of mercury) intra-alveolar pressure. This implies a correspondingly low surface tension. In fact, investigations in the last decade have revealed the presence of a thin mucoprotein film covering the alveolar surface (Clement *et alii*, 1958). The surface tension of this film with the lungs in resting position is about one-seventh that of water. This means that if there was a water film replacing the mucoprotein film, the pressure required to keep the alveoli expanded would be

airways and be drawn into further groups of alveoli. This is why in these cases fluid-filled alveoli are seen next to atelectatic areas.

In summary, some consequences of fluid-induced airway obstruction are variable, depending on the origin and the viscosity of the fluid, the condition of the patient, and some other factors. Atelectasis may occur immediately, may be delayed or may not occur at all. X-ray examination of the chest—the only objective method used in the assessment of these patients—can be expected to be informative only in some of the cases. Methods capable of detecting closure of the terminal airways independent of the development of atelectasis would appear to be more reliable.

## LUNG COMPLIANCE AS A MEASURE OF ATELECTASIS

As is well known, the lung requires the application of a certain negative pressure normally provided by the chest wall to maintain expansion. In the normal range of breathing the alterations in volume and pressure are

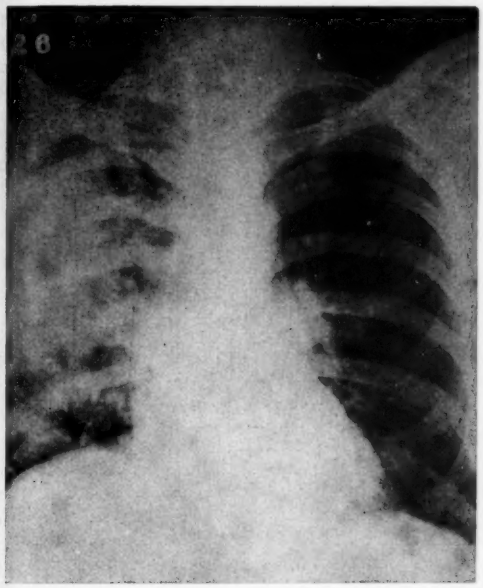


FIGURE II

Severe hæmoptysis. (By the courtesy of the Radiology Department, Royal Prince Alfred Hospital, Sydney)

proportional. The change in volume per unit of pressure across the lung is known as lung compliance (Mead and Whittenberger, 1953). Compliance therefore equals the relative ease with which pressure distends the lungs:

$$\frac{\text{volume changes in litres}}{\text{pressure changes in cm. } H_2O} = \text{compliance.}$$

One factor which must affect the value of compliance is the amount of lung subjected to distension. The range of lung tension in man and in the guinea-pig is the same, but quite obviously more air is required to bring about a given pressure in man. Similarly, twice as much air is needed for two lungs as for one. If some tributaries are completely blocked, compliance is decreased approximately in proportion to the amount of lung excluded (Mead and Collier, 1959). The measurement of lung compliance therefore is a suitable method of assessing the consequences of fluid aspiration, as an index of the amount of collapsed lung.

### *The Effect of Fresh Water in the Lung*

We have made this assumption in interpreting the results of our experiments. One millilitre of water per kilogram of body weight was injected into the trachea of lightly anæsthetized, intubated sheep; changes in ventilation, circulation (Halmagyi and Colebatch, in the press) and lung mechanics (Colebatch and Halmagyi, to be published) were measured. The amount of fluid injected intratracheally was equivalent to half a cup of water aspirated by a man.

The above-mentioned quantity of fluid caused a gross fall in lung compliance (Figure VI). If decrease in compliance is taken as an index of the amount of lung obstructed, and if allowance is made for some compensatory overinflation, it is likely that closure of about half of the lungs has occurred. Hyperventilation superimposed upon the stiffening of the lung resulted in a marked increase in the (elastic)

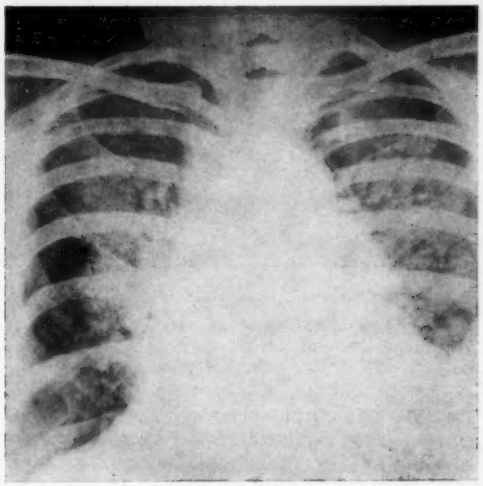


FIGURE III

Heart failure, pulmonary œdema. By the courtesy of the Radiology Department, Royal Prince Alfred Hospital, Sydney)

work of breathing (Figure VI). This accounts for the severe dyspnœa experienced by patients after inhalation of fluid. There was no evidence of bronchoconstriction.

If blood continues to perfuse the non-ventilated (obstructed or collapsed) alveoli, venous admixture is bound to result (Berggren,

1942). By calculating the proportion of the shunted blood, or by measuring arterial oxygen saturation, we theoretically should be able to assess the magnitude of the obstructed areas in the lung.

After the inhalation of 1 ml. of water per kilogram, arterial oxygen saturation in our animals dropped to a level roughly equivalent to that seen on the top of Mount Everest. This was the result of venous admixture, which represented a considerable proportion of the

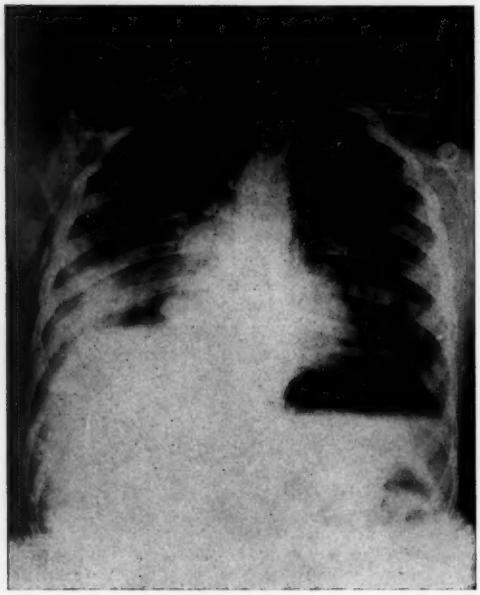


FIGURE IV

Crush injury of the chest in a boy, aged 11 years. (By the courtesy of Mr. Rowan Nicks, Page Pavilion, Royal Prince Alfred Hospital, Sydney)

total cardiac output (Figure VI). While compliance changes indicated the closure of about one-half of the lungs, the increase in shunt implied that oxygen uptake was still undisturbed in approximately two-thirds of the lungs. This discrepancy can be satisfactorily explained.

Hypoxia has long been known to result in pulmonary hypertension (Beyne, 1942). It has also been demonstrated that hypoxic pulmonary vasoconstriction is the result of a local chemoreflex involving vessels supplying the actually hypoxic alveoli (Euler and Liljestrand, 1946). Unilateral hypoxia has been shown to cause some redistribution of blood flow towards the well-oxygenated areas in all species investigated (Borst *et alii*, 1957; and others). The perfusion of atelectatic areas was found to be even more reduced than that of the hypoxic alveoli, which emphasized the importance of mechanical factors (Peters and Roos, 1952). However, the decrease in the perfusion rate of atelectatic areas is a gradual one; it is hardly perceptible in the first minutes, and develops into a near-complete obstruction after some days (Björk and Salén, 1950). This redistribution of blood flow from the non-ventilated towards the well-ventilated parts of the lungs is an important homœostatic mechanism of the pulmonary circulation. It allows a minimal increase in venous admixture in cases in which parts of the lungs are excluded from ventilation. This is why the size of obstructed areas will be somewhat underestimated by measuring only venous admixture or arterial oxygen saturation. If this measurement is carried out in recent obstruction, the estimate will be reasonably close to the real value; the possible error increases with time.

It has been demonstrated that in the normal lung one arteriole supplies many alveoli and capillaries may cross more than one alveolus (Knisely, 1960). It is also known that a considerable part of the capillary bed is closed at rest and is opened up only by an increase in overall or regional blood flow (Halmagyi, 1957). This multiplicity and reserve capacity of the pulmonary vessels would appear to explain why a loss of less than 50% of the functioning alveoli is compensated for in the normal lung and does not result in a perceptible increase in venous admixture (Colebatch and Halmagyi, to be published). In a diseased lung, this compensation can hardly be expected to occur. In chronic bronchitis, for example, a considerable portion of the terminal airways is occluded. If in this condition aspiration of fluid or a further increase in bronchial secretion occurs, further groups of alveoli will collapse. The number of those remaining open will be insufficient to compensate for this further loss, and severe hypoxæmia will inevitably result. In emphysema, on the other hand, the number of patent capillaries is significantly reduced (Isaakssohn, 1871). Abundant secretions in an acute chest infection will obstruct a large number of alveoli scattered around the lung at random. The loss of reserve capillaries and the loss of the multiplicity of alveolar blood supply will in this case be the principal factor preventing compensation, with resultant severe hypoxæmia (Platts and Greaves, 1957). This mechanism is shown schematically in Figure VII.

Pulmonary hypertension is a further, hitherto unknown result of the aspiration of small qnantities of fluid (Halmagyi and Colebatch,

in the press). The increase in pulmonary artery pressure is considerable, persists for about an hour and is due to the constriction of the pulmonary arterioles; pulmonary "capillary" pressure remains virtually unchanged. This effect is not caused by hypoxæmia; it rather appears to be related to a neuro-humoral mechanism, the details of which are at present under investigation. The onset of pulmonary hypertension offers a reasonable explanation for the right ventricular dilatation found in victims of drowning, as opposed to the left ventricular dilatation characteristic of suffocation (Donald, 1955). It also explains the occurrence of right ventricular failure in patients who inhale fluid. This mechanism should be included among the causes of pulmonary hypertension in lung disease.

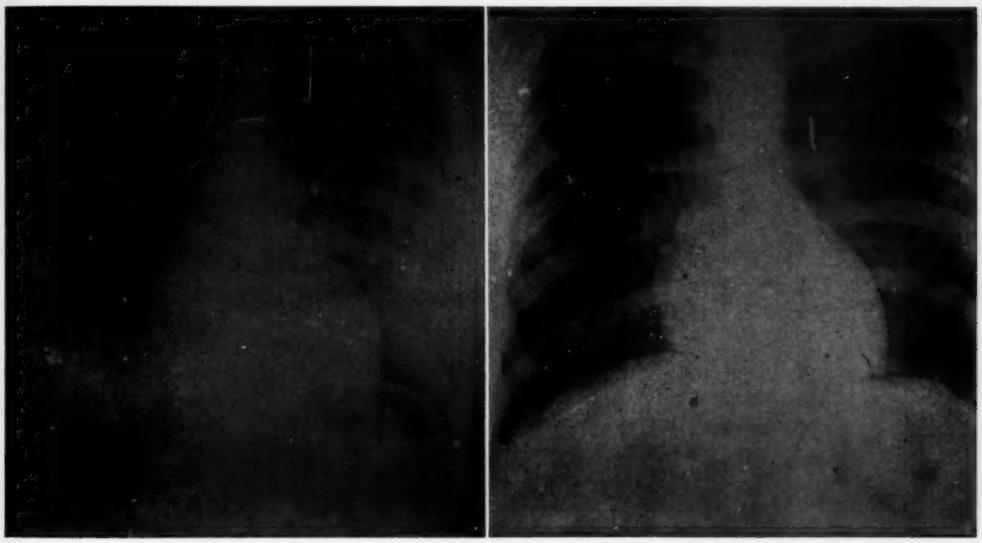
### *Physiological Responses to Other Solutions in the Lung*

The effect of fluids other than fresh water were also investigated. Sea water (Halmagyi and Colebatch, in the press; Colebatch and Halmagyi, to be published), saliva, gastric juice, amniotic fluid and blood (unpublished) were administered intratracheally to sheep, in the same dosage. It was surprising to find that the low pH of the gastric juice made little difference to the effect. Compliance and arterial oxygen saturation in an animal one week after the intratracheal administration of gastric juice (pH 2·0) were found to be normal. The inhalation of blood showed a marked difference in one respect: despite a comparable fall in compliance and arterial oxygen saturation, pulmonary arterial pressure remained unchanged.

### *Comment*

Though there are many interesting effects of various fluids in the lungs, the basic features can be illustrated by a comparison of sea water with fresh water. One millilitre of fresh water per kilogram injected into the trachea was completely absorbed within five minutes (Halmagyi, in the press). The same quantity of sea water—3·6% saline or four times the osmotic pressure of the plasma—led to the accumulation of more fluid in the lungs. After 20 minutes, the amount of water in the lungs was four times the quantity of sea water originally introduced. The initially hypertonic sea water was made isotonic by the depletion of plasma water, and its complete reabsorption might be expected to take hours.

If the physical properties of the fluid are the cause of closure of a large part of the lung, one would expect the effects observed to be related to the composition of the fluid inhaled. The



(*a*) (*b*)

FIGURE V

Blast injury of the lungs: (*a*) at admission; (*b*) 14 days later—recovery. (By the courtesy of Dr. Maurice Joseph, Page Pavilion, Royal Prince Alfred Hospital, Sydney)

effects of fresh water should last only a few minutes, whereas in the case of sea water the changes should persist. These predictions were only partly confirmed. There was no significant improvement in lung compliance or venous admixture 30 minutes after the introduction of fresh water (Figure VI). In general, the measurements showed little difference between the effects of fresh and sea water at 30 minutes.

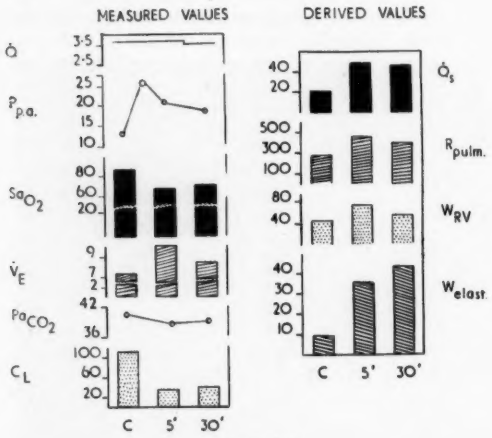



FIGURE VI

The effect of the intratracheal injection in sheep of 1 ml. of fresh water per kilogram. (Mean of 10 experiments.) Explanation of symbols: $\dot{Q}$, cardiac output, lit./min./m.² BSA; $\bar{P}_{p.a.}$, pulmonary arterial pressure, mm. Hg; $Sa_{O_2}$, arterial oxygen saturation *per centum*; $\dot{V}_E$, ventilation, lit./min./m.² BSA; $Pa_{CO_2}$, arterial carbon dioxide tension, mm. Hg; $C_L$, lung compliance, ml./cm. water; $\dot{Q}_s$, shunt, in percentage of cardiac output; $R_{pulm.}$, pulmonary arterial resistance, dynes sec. cm.$^{-5}$/m² BSA; $W_{RV}$, right ventricular work in arbitrary units ($\bar{P}_{p.a.} \times \dot{Q}$); $W_{elast.}$, elastic work of breathing, m./kg./min. $\times 10^{-3}$; C, control period; 5' and 30', 5 and 30 minutes following the intratracheal administration of fluid

This result may in part be due to anæsthesia. Once collapsed, the terminal airways and alveoli require a pressure related to their diameter to produce opening (Clement *et alii*, 1958). The anæsthetized animal tends to breathe at a fixed tidal volume, and though with light anæsthesia there may be occasional breaths larger than others, the pressure across the lung cannot be expected to reach a level required for complete reinflation. Similar considerations apply to the anæsthetized or unconscious patient, who is particularly susceptible to aspiration of fluid. Recent work indicates that the terminal air spaces in the lungs are an unstable system and require an occasional large inflation to maintain expansion (Mead and Collier, 1959; Ferris and Pollard, 1960). In the conscious state we take an occasional deep breath or sigh; in unconscious subjects or patients being artificially ventilated, periodic large inflations would appear to be desirable to prevent collapse.

Inflation of the lungs to a pressure of 40 cm. of water is normally adequate to produce complete expansion. In our experiments, the response following inflation to this level of pressure half an hour after the introduction of fluid allowed differentiation between the effects of sea and fresh water. As expected, improvement was observed in all animals during the actual period of intermittent positive-pressure breathing irrespective of the type of fluid inhaled. The difference became conspicuous only after the positive-pressure breathing was discontinued. At this stage the improvement was maintained in animals which had received fresh water, whilst a deterioration occurred in the sea-water group. The latter effect may well be attributed to the more widespread distribution, by inflation, of the fluid that had accumulated in the lungs of the animals given sea water. The likelihood of deterioration

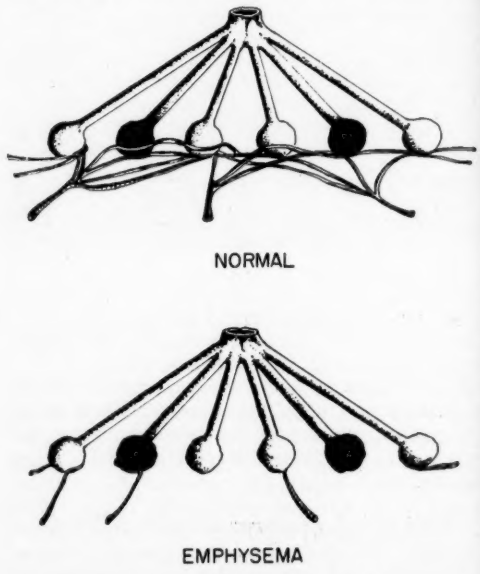



FIGURE VII

Schematic drawing to indicate the loss of the multiplicity of alveolar blood supply in emphysema. Black alveoli are obstructed. In the normal lung, capillaries perfusing the obstructed alveoli also supply normal ones; no venous admixture can be expected. In the emphysematous lung the number of capillaries is reduced; the blood perfusing a non-ventilated alveolus has no chance to be oxygenated in another normal air sac; venous admixture is bound to result

following the inflation is an important consideration in resuscitation.

From the example of sea water, it appears clear that the presence of fluid may prevent a lasting reinflation of the lungs. It seems likely that a gross shut-down of terminal airways with venous shunting in the affected area will remain so long as the fluid is present. However, restoration was also incomplete in the fresh-water group at a time when theoretically all water had already been reabsorbed from the airways. This suggested an additional mechanism preventing the opening of the obstructed airways in the " drowned lung ".

Further information on this point was obtained from studies performed on vagotomized animals. Similar, though less marked, changes were observed to follow the introduction of sea or fresh water. In the case of fresh water, complete restoration of lung compliance and arterial oxygen saturation was obtained by inflation half an hour after the intratracheal administration of 1 ml. of fresh water per kilogram, though not with larger doses. Inflation in those given sea water was followed by deterioration similar to that seen in the non-vagotomized group. These results, and some other observations (to be published), indicate that the consequences of fluid aspiration are not due solely to the physical properties of the fluid, but appear also to involve a reaction producing closure in the terminal airways mediated by the nervous system. This reflex response to fluid is under further investigation.

### *Summary of the Physiopathology of the Drowned Lung*

In summary, hypoxæmia is the most important clinical consequence of fluid aspiration. The extent of hypoxæmia is not strictly dependent on the amount of fluid inhaled; relatively small quantities may have severe effects. Hypoxæmia is due to the passage of venous blood through non-ventilated areas. Obstruction to ventilation is probably due in part to the surface tension of the fluid, producing an unstable balance of forces in small airways and alveoli so that they close and collapse, and in part to reflex effects. Pulmonary hypertension, a further consequence of fluid aspiration, appears to be neuro-humorally mediated.

## MANAGEMENT OF DROWNED LUNG

The therapeutic implications of these findings are worthy of consideration. The requirements for resuscitation are dealt with in detail elsewhere (Colebatch and Halmagyi, to be published). The main points in treatment will be outlined here.

To overcome hypoxæmia, the closed parts of the lungs should be inflated, as far as this is possible, without damage to still expanded areas. The maximum safe inflating pressure should be available for artificial respiration or assisted breathing. From studies of the mechanical properties of the human lungs and thorax (Rahn *et alii*, 1946), 30 mm. of mercury (equal to 40 cm. of water) is a reasonable upper limit for adults. This should give an adequate safety margin, as the experimental work of Schaeffer *et alii* (1958) indicates that lung rupture and air embolism regularly occur when the pressure in the alveoli is 60 mm. of mercury or above that on the surface of the lungs.

A large inflation should be given to ventilate as much lung as possible; a relatively slow rate of 8 to 12 per minute will then be sufficient to maintain a normal level of alveolar ventilation. Under these circumstances, the expiratory phase may be four to six times as long as inspiration. This ensures a low mean airway pressure and so avoids any significant depression of cardiac output (Maloney and Handford, 1954; and others). In our experiments, a Royal Melbourne Resuscitator (manufactured by the Commonwealth Industrial Gases Co. Ltd.) proved to be adequate. Other breathing machines which allow the inflating pressure to build up to 30 mm. of mercury, with a rapid release of pressure at the end of inspiration and no resistance to expiration, would also be suitable. A negative-pressure phase adds complexity and promotes lung collapse at the end of each expiration without offering any advantage.

Oxygen inhalation is widely used to relieve hypoxæmia in patients who have aspirated fluid. Even in the absence of measurements, many authors have been impressed with the inadequacy of this treatment from clinical observation. This was confirmed in our own experiments. Breathing 100% oxygen did not restore arterial oxygen saturation to a satisfactory level, owing to the persistence of a gross alveolar shunt. On the other hand, when the animals' lungs were inflated in a manner indicated above, air was similarly inadequate even though the shunt was somewhat reduced. For restoration of normal oxygen saturation in the arterial blood, a combination of 100% oxygen with intermittent positive-pressure breathing was essential. The effect of oxygen was not simply due to an additional 2 volumes *per centum* of physically dissolved oxygen, as this would have raised the arterial saturation on average only 13% compared with air—that

is, from 65% to 80%. The full saturation (98%) achieved could have been due only to a further fall in the amount of blood passing through the non-ventilated areas. Oxygen-rich gas mixtures are known to relieve pulmonary arterial constriction. The dilatation of the pulmonary arterioles was the most probable mechanism, resulting in a redistribution of pulmonary blood flow towards the well-oxygenated areas.

The optimal duration of intermittent positive-pressure breathing will depend on the quantity and composition of fluid inhaled. With a periodical assessment of the patient's clinical state without positive-pressure breathing, one can decide how long the treatment should be continued.

There seems little reason to doubt that similar results would be obtained if a similar treatment was applied to humans who had suffered aspiration of fluid. In fact, intermittent positive-pressure breathing with 100% oxygen has been reported to be highly effective in patients with pulmonary œdema (Miller and Sproule, 1959), in which there are analogous changes in lung mechanics.

Though we have been able to suggest a way to overcome the acute respiratory embarrassment that follows aspiration of fluid, the severe effects of fluid in the lungs revealed in our studies underline the importance of prophylaxis and the control of secretions by the well-established methods of postural drainage and promotion of coughing. Nevertheless, emergencies will continue to arise. The prompt application of the principles outlined here will contribute to the control of otherwise fatal episodes.

## ACKNOWLEDGEMENTS

Experiments referred to in this review were supported in part by grants from the following bodies: the National Health and Medical Research Council of Australia; the Post-Graduate Medical Foundation and the Consolidated Medical Research Fund of the University of Sydney; the Joint Coal Board. Many parts of this work depended on the cooperation of the members of the technical staff of the department. It is with great pleasure that we acknowledge the work of Mr. P. Donelly, Mr. T. Miller, Mr. D. Fahey, Mr. W. Green and Miss Maureen Woodward. Our thanks are also due to the Department of Illustration of the University of Sydney. It was a privilege to enjoy Professor C. R. B. Blackburn's interest and support throughout these experiments.

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# Proceedings of The Royal Australasian College of Physicians

## ORDINARY MEETING, 1960

The Ordinary Meeting of the College was held in Sydney from October 12 to 15, 1960. It was attended by 150 Fellows and Members representative of all the Australian States and New Zealand. The President, Dr. T. M. Greenaway, was in the chair.

## SCIENTIFIC AND CLINICAL PROGRAMME

Two scientific sessions, two clinical meetings and a plenary session with the Australian Laennec Society were held in the Stawell Hall of the College, 145 Macquarie Street, Sydney.

### *Plenary Session*

A plenary session with the Australian Laennec Society was held on Wednesday, October 12, and took the form of a symposium on "Diffuse Lung Disease".

John Read opened the symposium with a paper entitled "Clinical and Radiological Aspects of Diffuse Lung Disease". He said that it was necessary to limit his discussion to a special group of lung disease in which there was new, abnormal tissue present throughout the lungs. He proposed a pathological classification, based on the anatomical sites of the abnormal tissue, and demonstrated that that classification had important physiological implications as far as respiratory function was concerned. There might be little or no correlation between radiological appearances and symptomatology. Important symptoms were dyspnœa, dry cough and weight loss. Physical examination might reveal no abnormality at all, or cyanosis, finger clubbing, limited chest expansion and scattered crepitations in the chest. Extrapulmonary signs might provide important clues to the diagnosis. Dr. Read said that a number of specific radiological features ought to be considered, but they were seldom diagnostic. In the approach to specific diagnosis, lymph-node biopsy and lung biopsy might play a part. The latter would provide a pathological, but often not an ætiological, diagnosis. Overall, not a great number of diffuse lung lesions of the type under discussion could be successfully treated, and many needed no treatment. In conclusion, a conservative but constructive approach to lung biopsy was urged.

In discussing "The Pathology of Diffuse Lung Disease", K. Viner Smith said that a disease pattern could be recognized in which the changes were in the alveolar walls, in the connective tissue of lobular septa and about the broncho-vascular bundles. In the early and reversible stage, the main features were capillary dilatation and proliferation, œdema and monocyte infiltration. Later there was proliferation of reticulin fibres in the alveolar walls, and later still collagen fibres were laid down. In the last stage there might be compact sclerosis of the lungs or the changes of honeycomb lung. There were variations in the speed of the process, in the volume of lung affected and in some minor histological details. In its later stages, that pattern of disease was often called diffuse interstitial fibrosis. That was an undesirable name, as it referred to an end state only, and could no more be used to describe a disease than could the term granular contracted kidney to which it was analogous. A preferable term would be chronic interstitial pneumonia. Some of the causes of that pathological pattern were known. They included some of the collagen diseases, especially scleroderma and rheumatic fever; some infections, including rickettsial; some chemicals; and irradiation. There remained a group of cases in which no cause could be found for the lung condition. Hamman and Rich had described four such cases in which the process was acute. Later authorities had widened the Hamman-Rich syndrome, and Scadding had stated that a large proportion of cases of unknown ætiology fitted into that syndrome. Dr. John Read had produced good evidence that some of the patients were suffering from a disordered immune process. Excluding the cases which Dr. Read described, Dr. Viner Smith said that the Hamman-Rich syndrome was, from the pathologist's point of view, not a distinct disease. It was a term which meant a chronic interstitial pneumonia of unknown ætiology.

"The Physiological Aspects of Diffuse Lung Disease" were discussed in a paper presented by John Read. This paper was to have been presented by Bryan Gandevia, who was prevented by illness from attending. Dr. Read said that there were two major physiological defects in the type of lung under discussion. The first was the increased stiffness or rigidity of the lung, which was reflected in a lowered compliance. The second was interference with the passage of oxygen from alveolus to capillary across the thickened alveolar-capillary membrane. The diffusion of carbon dioxide was not interfered with, and the patients did not develop carbon dioxide retention. Central cyanosis at rest did sometimes occur, and that could not be explained on the basis of a simple diffusion defect. A third functional abnormality—ventilation-blood flow imbalance—had to be invoked, and its presence had been demonstrated in such patients by means of the respiratory mass spectrometer. Formal tests of respiratory function, based on those abnormalities, were useful, firstly in demonstrating the presence or absence of a diffuse lung lesion in cases of doubt, secondly in assessing the nature of the incapacity and its extent, and thirdly in providing an objective measure of the effects of therapy. Simple ventilatory tests might show a reduced vital capacity, but no airway obstruction. The arterial oxygen saturation might be normal or low, and sometimes fell on exercise, but that was by no means a regular feature. Arterial carbon dioxide tension might be low or normal. None

of those investigations was sufficiently precise in difficult cases. Actual measurement of lung compliance might yield diagnostic information, but again the normal range was very wide. Dr. Read said that measurement of the diffusing capacity of the lung was not unduly difficult, and was by far the most sensitive method of detecting thickening of the alveolar walls.

Maurice Joseph presented a paper entitled "Causes of Hæmoptysis in 250 Patients", in which he discussed the causes of hæmoptysis in 250 patients seen in private and hospital practice in the last three years. He said that bronchiectasis had accounted for 29% of the cases, pulmonary tuberculosis for 22% and bronchial carcinoma for 12%, and in 11% the cause of the hæmoptysis had remained undetermined despite complete investigation. Those four groups thus comprised 74% of all cases. Twenty-four other causes were listed, and pneumonia, pulmonary infarction, chronic bronchitis, hypertension, mitral stenosis, secondary neoplasm, pulmonary abscess and hydatid disease were prominent. Mere streaking of the sputum with blood was not considered to be an hæmoptysis, and the patients included in the survey had coughed up at least a teaspoonful of blood. Some unusual causes were Wegner's granulomatosis and Goodpasture's syndrome, trophoblastic emboli, early pulmonary sarcoid and congenital absence of the right pulmonary artery. A follow-up investigation of the 28 patients who had had hæmoptysis of undetermined origin for periods of three months to three years, showed that not one subsequently developed overt pulmonary disease. Dr. Joseph suggested that, provided the initial investigation was complete, and included bronchoscopy and adequate bronchography, the likelihood that serious pulmonary disease would be overlooked was small.

"Some Persisting Problems in Tuberculosis" were discussed by W. L. Forsyth. He emphasized the fact that 4000 new cases had been reported throughout Australia during the financial year 1959–1960. That was a slightly higher figure than that for the previous year, owing to increases in New South Wales and Victoria. The notification rate was 39·1 per 100,000 of population; and Federal grants to the States for tuberculosis purposes, together with Repatriation Department costs, amounted to over £7,000,000 for the year. He defined a "case of tuberculosis" as one requiring medical or administrative action, following the definition proposed at the World Health Organization Seminar held in Sydney in June, 1960. The changing balance in treatment from the in-patient to the out-patient field was discussed, with its attendant problems of staffing and technical services. The current importance of compulsory mass X-ray surveys was mentioned, and it was pointed out that, together with State chest clinics, they were responsible for about half the notifications. The other half was supplied by hospitals and private practitioners. The surprising results of tuberculin surveys in North Queensland children were demonstrated. The very high positive figures in those areas were thought likely to be caused by skin sensitivity to rapidly growing mycobacteria, and not to the human tubercle bacillus. The results of skin sensitivity tests with purified protein derivatives from other mycobacteria were shown, material for the tests having been obtained from the United States of America. The results were somewhat mixed, but it seemed clear that mycobacteria other than the human tubercle bacillus were causing tuberculin skin sensitivity in Queensland. Two cases of pulmonary disease accompanied by rapidly growing mycobacteria in the sputum were presented. The response to treatment in both was satisfactory. In one case lung tissue was resected, and the histological picture was indistinguishable from that of conventional tuberculosis. Acid-fast bacilli were seen in the sections, but could not be grown from the resected specimen. The problems raised by out-patients who failed to adhere to drug schedules were discussed, and the importance of testing urine for drugs was emphasized.

*First Scientific Session*

At the first scientific session held on Thursday, October 13, the following contributions were presented.

In a paper entitled "A Study of Chromosomes in Leukæmia and Similar Disorders", by Professor H. N. Robson and M. A. Kinlough, Dr. Kinlough said that a simplified technique for the study of human chromosomes in bone marrow cells had been developed, by which preparations could be made without the use of tissue culture. That technique was then described. By the use of the technique, the chromosomes had been studied in cases of leukæmia, polycythæmia vera, myelomatosis and similar disorders. Dr. Kinlough said that the present technique had the advantage that the in-vivo situation was being studied directly, to obviate possible changes arising during the culture period. Findings so far indicated that there was no consistent alteration in the number of chromosomes in leukæmia, and that such findings, when culture techniques were used, might well be artefactual.

D. W. Piper presented a paper entitled "A Radiographic Study of the Hepatic and Portal Veins in Cirrhosis". He said that one of the problems in the study of liver disease had been that portal vein obstruction did not produce ascites, whereas hepatic vein obstruction produced marked ascites and a picture resembling that seen clinically in cirrhosis. As the relative degree of hepatic and portal vein obstruction in cirrhosis had not been determined, a study was made of those two venous systems in a series of cirrhotic livers. The livers were injected with a radio-opaque material consisting of bismuth oxyiodide and gelatin. The hepatic vein was injected in one lobe and the portal vein in the other lobe. In normal livers, both veins filled completely and a normal pattern of filling had been defined. In the cirrhotic livers, there had been defective filling of the hepatic vein, and the large and particularly the small tributaries were distorted and irregular; small saccular dilatations were seen on some branches. Some abnormality was present in 11 of 12 cases studied. In no case had any abnormality been seen in the portal vein. There was no correlation between the pathological and clinical features of the case and the degree of X-ray change. It was concluded that in cirrhosis the vein predominantly obstructed was the hepatic vein, and that finding had been discussed in relation to clinical features of cirrhosis. The nodular regeneration and fibrosis of cirrhosis led to hepatic vein obstruction. That produced a high sinusoidal pressure, which resulted in portal hypertension, ascites and further liver cell damage. That observation—that hepatic vein obstruction probably played a major part in the production of clinical features of cirrhosis—was consistent with animal experiments on portal and hepatic vein obstruction and recent observations at operation on the venous pressure changes in cirrhosis.

In a paper by D. F. J. Halmagyi and H. J. H. Colebatch entitled "The Rigid Lung of Pulmonary Embolism: The Mechanism of Respiratory Embarrassment", Dr. Halmagyi said that respiratory distress, cyanosis and pulmonary hypertension had been recognized more than half a century ago as characteristic features of pulmonary embolism, but their mechanism

was still controversial. Since the circulatory and respiratory phenomena could not be investigated in patients, they had been studied in sheep, after the intravenous administration of graded amounts of embolic material. The most surprising finding had been a very rapid drop in lung compliance, indicating a widespread closure of the terminal airways, and the exclusion of a major proportion of the alveoli from ventilation. The lungs were not only extremely rigid, but also resistant to reinflation. The sudden increase in lung rigidity appeared to be the cause of respiratory distress in pulmonary embolism. The hitherto ill-understood cyanosis might be accounted for by perfusion of non-ventilated areas. A closure of respiratory units as a response to vascular obstruction was a new aspect of the relation between circulation and respiration in the lungs, and could affect the therapeutic approach to pulmonary embolism.

W. A. Seldon presented a paper, in conjunction with C. Rubinstein and A. Fraser, entitled "The Incidence of Atrial Septal Defect in the Metropolitan Area of Sydney as Determined by a Mass X-Ray Survey". He said that during a mass X-ray survey of the metropolitan area of Sydney, 501,973 persons out of a total population of 890,411 above the age of 14 years had been radiologically examined on 70 mm. films. All those showing radiological evidence of congenital or mitral valvular heart disease were recalled for clinical examination, and a large number were referred to cardiac departments of general hospitals for further investigation. On examination, 24 patients were found to have signs of atrial septal defect, and in most of those patients the diagnosis had since been confirmed by further investigation, including cardiac catheterization. On the assumption that the incidence was the same in the population not radiologically examined, and if allowance was made for an 88% yield from the X-ray films, there would be 49 cases of previously unsuspected atrial septal defect in the total population of 890,411. In addition, a search of the records of the major Sydney hospitals revealed 56 patients with atrial septal defect resident in the area covered by the survey. None of that number had volunteered for X-ray examination as they were already under observation, and five other patients from the same areas had attended private cardiologists only. That gave a total of 110 cases in the population of 890,411, an incidence of 12 per 100,000 or one per 8,000. If it was assumed that the incidence of atrial septal defect was uniform throughout Australia, there would be 1240 cases in the whole of the Commonwealth.

In a paper entitled "Tobacco Smoking and Ventilatory Function in an Australian Population", by John Read and T. Selby, Dr. Selby said that in that survey 300 ambulant subjects had been interviewed in the out-patient department of a general hospital (patients from selected clinics, visitors, staff). A record had been obtained of family history, personal respiratory history, smoking history, and the presence or absence of cough and sputum. The ventilatory function of the lungs was assessed by the use of the Wright Peak Flow Meter. It was noted that that was the first study of the effects of smoking on respiratory function under Australian conditions; and in the analysis of results, account had been taken of factors which had been largely ignored in the few overseas studies. Normal standards were determined for non-smoking males and females without cough and sputum, and were correlated with age and body stature. On that background, the patterns of ventilatory function with increasing age had been studied in various groups of male and female smokers, and in non-smokers with symptoms. Dr. Selby said that the following points could be demonstrated for the first time: (i) Smoking, in the absence of symptoms, did not lead to any steady deterioration in ventilatory function with increasing age. (ii) In both smokers and non-smokers, the presence of cough and sputum was associated with a steady deterioration in ventilatory function with increasing age. In the case of smokers, that deterioration was not necessarily permanent, as illustrated by the findings among ex-smokers. (iii) Some factor other than prolonged smoking alone was necessary for the production of the bronchitis-ventilatory insufficiency syndrome.

At the second scientific session held on Friday, October 14, the following contributions were presented.

A paper entitled "Serum Vitamin $B_{12}$ Levels in Chronic Gastritis and the Development of Pernicious Anæmia", by Ian Wood, D. C. Cowling, B. Ungar and Miss A. Gray, was presented by Ian Wood. Dr. Wood said that cases of severe chronic atrophic gastritis, proved by serial histamine test meal examinations and gastric biopsies, had been studied over the past twelve years. Some patients had shown falling vitamin $B_{12}$ levels, and two, who had entered the pernicious anæmia range, had shown symptoms and deficient absorption of $^{58}$cobalt-labelled vitamin $B_{12}$. As a result of those studies, it had been concluded that there were three clinical states—pre-pernicious anæmia, latent pernicious anæmia and overt pernicious anæmia.

Athol Robertson presented a paper in conjunction with Mervyn Cheong entitled "Iron Deficiency Anæmia Treated with an Intravenous Iron Compound". In this paper a series of 30 cases studied in hospital and private practice was reviewed. The preparation used was "Astrafer I.V.", a compound of ferric iron, combined with dextrin molecules of less than 5000 M.W., and supplied as a solution containing 20 mg. of iron per cubic millilitre. The first 12 subjects were hospital in-patients, and detailed peripheral blood, bone-marrow and serum-iron estimations were performed before, during and after treatment. In nine cases the anæmia had been due to chronic blood loss, and in three cases to deficient diet. Daily doses of 100 mg. of iron produced a good response in all cases, but two patients had toxic reactions after single doses of 200 mg. of iron. The largest total dose given was 1400 mg. of iron, and the smallest was 750 mg. A reticulocyte peak occurred between the fifth and ninth days of treatment. The highest peak was 26% on the sixth day of treatment of a man, aged 79 years, with chronic blood loss. With the use of the experience gained in those 12 cases, a further 18 patients were treated, clinical and peripheral blood examination being mainly used as criteria for diagnosis. The majority of those patients were anæmic from chronic blood loss, whilst the remainder did not have a demonstrable cause for their anæmia. All patients showed a satisfactory final hæmoglobin increase, and no general or local reactions had been observed with daily injections of 100 mg. of iron. A single reticulocyte count was performed about the seventh day of treatment, and the failure to demonstrate a marked rise in reticulocytes was believed to be due to missing the peak response by that arbitrary method. The authors concluded that that intravenous iron compound provided an effective and certain treatment of iron-deficiency anæmia. When used in single daily doses of 100 mg. of iron or less for adults, it appeared to be free from undesirable local or general reactions. In several cases the treatment had been almost as dramatic in effect as blood transfusion.

"Guanethidine ('Ismelin'): Clinical Trial of a New Hypotensive Agent" was the subject of a paper presented by Douglas Stuckey. He said that the

hypotensive properties of guanethidine had first been reported by Maxwell *et alii* in 1959. The drug was thought to act by inhibiting the release of chemical mediator substances from sympathetic nerve endings, and exerted its hypotensive effect in the same way as the ganglion-blocking agents. Twenty severely hypertensive patients had been treated over periods of two to six months. All had control estimated mean arterial pressures of 150 mm. Hg or more, and in seven patients the figure was more than 170 mm. Hg. Three had suffered from a previous cerebro-vascular accident, and six from attacks of left ventricular failure. Evidence of renal failure was present in five patients, and four had frank malignant hypertension with papillœdema. Grade III retinopathy was present in an additional four patients. Treatment was initiated with chlorothiazide and reserpine, or if the latter drug was not well tolerated, with hydralazine. If blood-pressure control was inadequate guanethidine was then added, the dose commencing with 25 mg. per day and being increased at intervals of four to seven days. Long-term blood-pressure control was assessed as excellent in four cases, good in six, fair in eight, poor in one, and unsatisfactory in the other. Those results compared favourably with those of similar series treated with mecamylamine. The average daily dose of guanethidine was 75 mg., with a range of 12·5 to 175 mg. Transient undesirable hypotensive effects (faintness, syncope, angina) were noted in seven cases. Diarrhœa, the only troublesome side-effect, occurred in five cases, and in three it was severe and persistent, preventing the effective use of the drug in treatment. Other uncommon and minor side-effects were muscle weakness, tremor, joint pains and visual disturbances. Drug tolerance had not been encountered so far, and the hypotensive effect was regular and predictable in a given case. It was confirmed that guanethidine was an effective hypotensive agent in the majority of cases, and Dr. Stuckey noted that, if tolerance did not develop, the drug should prove useful in the long-term management of severe hypertension.

A paper entitled " Effect of Long-Term Anticoagulant Therapy on Liability to Recurrent Cerebral Vascular Episodes " was presented by David C. Wallace. He said that Elkington, in his Lumleian Lectures of 1958, had suggested that a controlled clinical trial of the effects of long-term anticoagulant therapy in cases of cerebral vascular disease could be carried out in an institution dealing with the chronically ill. With the approval of the Department of Medicine at the University of Melbourne, an attempt had been made to do this at the Greenvale Village for the Aged, an institution for the chronically infirm elderly. All patients in the institution who had had a definite cerebral thrombosis and who were not excluded by any condition which would contraindicate anticoagulant therapy were included regardless of age. They were divided at random into two groups, and new patients were included as they were admitted to the hospital. One group was given prolonged anticoagulant therapy, phenindione (" Dindevan ") being used as the anticoagulant of choice ; but when sensitivity to that drug developed, warfarin (" Marevan ") was employed. The trial covered a period of 21 months, and dealt with a personally observed series of 52 cases, 27 in the treated series and 25 in the control series. The two series were closely comparable in regard to age, sex, blood pressure, degree of infirmity and the length of time under observation, which averaged nearly ten months. Apart from the difference in treatment (with anticoagulants), all other factors which might have been significant, such as diet, environment, degree of activity, etc., were uniform. Patients who left the institution were regarded as having left the trial, as it was found impossible to be sure of their continuing treatment or of the occurrence of complications. Post-mortem examination was performed on 11 of the 12 who died during the investigation. Hæmorrhagic complications were relatively frequent in the treated series, but with the exception of two cerebral hæmorrhages they were of minor importance. Hæmorrhagic complications were by no means absent in the controls, and included one cerebral hæmorrhage. Dr. Wallace noted that there were three patients in the treated series who had a further cerebral vascular accident, and 10 in the untreated group. By the use of Yates' correction for continuity in small series, $\chi^2$ could be calculated to equal 4·34 for that collection of data, and thus the probability of this result occurring by chance, if there was no difference in the two treatments, would be between one in 20 and one in 100. If cerebral thrombosis alone was considered, there were two such episodes among the 27 treated patients and nine among the 25 untreated patients. In that instance $\chi^2$ equalled 4·76, and once again the probability of the result occurring by chance lay between one in 20 and one in 100. Dr. Wallace said that those figures did not take into account multiple cerebral vascular accidents which occurred in single patients. There the ratio was four in the treated patients to 11 in the untreated group, and that result could not be subjected to $\chi^2$ analysis. It was concluded that Elkington's question had now been answered. It had been shown in an adequately controlled investigation of the effects of long-term anticoagulant therapy, carried out in an institution for the chronically ill, that that treatment did indeed lower the incidence of recurrent cerebral vascular accidents.

The concluding paper of these scientific sessions was " Physicians, Psychiatrists and General Practitioners ", presented by David C. Maddison. Dr. Maddison said that the paper constituted a brief report of a training programme which had been designed to give general practitioners a deeper understanding of the problems of the doctor-patient relationship, with particular reference to the diagnosis and treatment of psychogenic illness in general practice. The practitioners had met for 25 weekly sessions, the substance of the meetings being free discussion of cases from their own practices, along the lines developed by Michael Balint. The major problems which were recognized arose from the reluctance of doctors as a group to diagnose psychogenic illness, and their even greater reluctance to enter into a therapeutic relationship with such patients. The most fundamental bases for those difficulties lay in their awareness of the involvement of their own emotions in psychotherapy, and a fear of closeness to their patients which a psychotherapeutic approach might bring. The complicated unconscious components of the relationships between general practitioners and their consultants were also touched upon. The paper strongly emphasized the appalling inadequacy of the preparation received by general practitioners and physicians relative to the incidence of neurotic and psychosomatic disorders in the practice of medicine.

## CLINICAL MEETINGS

Two clinical meetings were held in the Stawell Hall of the College in Macquarie Street, Sydney, on Thursday, October 13, and Saturday, October 15. At the first clinical meeting the following contributions were presented: "Hyperparathyroidism with Peripheral Neuritis due to Parathyroid Adenoma", by Professor C. R. B. Blackburn and R. Beal (by invitation); "Hyperparathyroidism Complicated by Pancreatitis", by D. W. Piper and Miriam Stiel (by invitation); "Primary Aortic Arteritis", by A. M. Lloyd and Douglas Stuckey; and "Familial Mitral Stenosis with Unusual Features", by G. E. Bauer. At the second clinical meeting the following contributions were presented: "Primary Aldosteronism", by Professor R. B. Blacket; "Temporal Lobe Epilepsy", by E. L. Davis; "Generalised Actinomycosis", by Clement Boughton; and "Collagen Disease with Polymorphous Skin Lesions", by Ronald Lewis.

## MEMBERSHIP

*Admission of Members.* The following candidates, who were successful at the examinations held in Sydney in October, 1960, were presented by the Censor-in-Chief to the President, who, in the presence of the Council and Censors of the College, formally admitted them to Membership: J. E. Edwards, John Ferguson and E. D. O'Callaghan, of Queensland; A. G. Collins, R. L. Hodge, D. A. Kennedy and T. A. White, of South Australia; John K. Dawborn, J. E. Gault and B. C. Ritchie, of Victoria; D. H. Gutteridge, of Western Australia; and John S. Duke, Miles T. Havyatt, Ian J. Mackie, F. L. Rothwell and G. S. Walker, of New South Wales.

*Honours.* The congratulations of the College are extended to Sir Macfarlane Burnet, of Melbourne, a joint winner of the Nobel Prize for Medical Science in 1960. The following Fellows have been the recipients of honours bestowed by Her Majesty the Queen: Sir Alfred Rowden White, of Melbourne, Knight Bachelor; Professor Sydney Sunderland, of Melbourne, Companion of the Most Distinguished Order of St. Michael and St. George; Dr. Edward Holbrook Derrick, of Brisbane, Commander of the Most Excellent Order of the British Empire.

*Obituary.* Council records with regret the death of Dr. S. A. Smith, of Sydney, a Founder of the College and President from 1946 to 1948; of Professor J. G. Hayden, of Melbourne, a Founder of the College and President from 1958 to 1960; of Major-General Sir Fred Bowerbank, K.B.E., of Wellington, and Sir Samuel Burston, of Melbourne, who were Foundation Fellows of the College; and of Dr. G. R. Beattie, a Member of the College from Hobart.

*Membership.* The College now has a roll of 11 Honorary Fellows, 360 Fellows and 638 Members.

## GENERAL

*Appointment to Editorial Committee.* Dr. John Beveridge has been appointed to a vacancy created on the Editorial Committee by the resignation of Dr. H. M. Whyte.

*Travelling Scholarship in Medicine, 1961.* The Travelling Scholarship in Medicine for 1961 has been awarded to Dr. Otto Appenzeller.

*Roche Research Fellowship.* The Roche Research Fellowship of The Royal Australasian College of Physicians for 1961 has been awarded to Dr. Boleslaw Starzecki, of Sydney.

*Pfizer Travelling Fellowship.* The Pfizer Travelling Fellowship in Clinical Medicine will in future be awarded as a Fellowship of The Royal Australasian College of Physicians.

*Jubilee Fund Study Grants.* Two study grants, each having a value of £750 Australian, will be awarded for overseas travel in 1961.

*Examination for Membership.* A by-law was introduced by Council in October, 1960, whereby Members of the Royal College of Physicians of London may apply for exemption from the written papers of the Membership examination of this College. Reciprocity now exists between the two Colleges regarding exemption from the written papers. Intending candidates are advised that they must make application to the respective Colleges.

*Gifts.* The portrait of Professor E. G. Sayers by William Dargie, which was presented to the College by the New Zealand Fellows and Members, has been hung in the College. The College also acknowledges with appreciation gifts of silverware from Dr. W. G. C. Paterson and Douglas Miller, Esq., F.R.A.C.S. Gifts to the Library have been received with appreciation from Dr. Torry Spark, the late Dr. John F. Fulton, Dr. Bryan Gandevia, Mrs. Wilfred Fairfax, the Queensland Institute of Medical Research, Dr. F. Hales Wilson, Major-General Sir Fred Bowerbank, W. W. Woodward, Esq., F.R.A.C.S., Dr. A. R. Southwood, Mrs. M. Hill, Dr. Michael Kelly and Dr. Theo G. Gray.

*Jubilee Fund.* The Council acknowledges with appreciation gifts to the Jubilee Fund from Australian Fellows and Members, which in the year ended October 10, 1960, totalled £16,190 12s. 5d.

*Representatives of College.* The following have been appointed to represent the College: Dr. J. J. Billings, of Victoria, on the National Health and Medical Research Council; the President, Dr. Eric Clarke and Dr. H. Maynard Rennie at the Convention to discuss the constitution of the proposed Australian Medical Association; Professor J. G. Hayden, Dr. J. J. Billings, Dr. Clive Fitts, Dr. A. V. Jackson and Dr. Bryan Gandevia to submit evidence at hearings of the Committee on the Dillon Report.

*Future Meetings.* The venue of meetings of the College between 1961 and 1964 has been rearranged and will now be as follows. In 1961, the Annual Meeting will be held in Perth on May 1 to 3, and the Ordinary Meeting in Adelaide in the week commen ng October 9. In 1962, the Annual Meeting will not be held in view of the Australasian Medical Congress to be held in Adelaide in May; the Ordinary Meeting will be held in Melbourne. In 1963, the Annual Meeting will be held in Sydney and the Ordinary Meeting in Brisbane. In 1964, the Annual Meeting will be held in New Zealand.

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